EXHIBIT 45

WACHOVIA CAPITAL MARKETS, LLC
EQUITY RESEARCH DEPARTMENT

Connetics Corp. (CNCT-NASDAQ)

CNCT: Uncert. In Velac Could Create Price Pressure--Lower Est.

Q1 In-Line

Market Perform
April 26, 2005
Price $27.57
52 Wk. Rng. $31-17

Earnings Estimate Revised Down

EPS	2004A		2005E		2006E		REV	2005	2006
Q1 (Mar.)	$0.05	NC	**$0.03**	**A $0.02**	NE	NC	$42.4	MM	NE
Q2 (June)	0.19	NC	**0.08**	**0.12**	NE	NC	46.1		NE
Q3 (Sep.)	0.10	NC	**0.27**	**0.23**	NE	NC	47.5		NE
Q4 (Dec.)	0.16	NC	**0.29**	**0.42**	NE	NC	48.8		NE
Full FY	$0.51	NC	**$0.69**	**$0.80**	**$0.97**	**$1.18**	$184.8	MM	$230.9 MM
FY P/E	54.1x		40.0x		28.4x				
Full CY	$0.51	NC	**$0.69**	**$0.80**	**$0.97**	**$1.18**			
CY P/E	54.1x		40.0x		28.4x				

Source: Company data and WCM, LLC estimates NA = Not Available, NC = No Change, NE = No Estimate, NM = Not Meaningful

Shares Out.: (MM)	38.0	LT Debt: (MM)	$240.0
Market Cap.: (MM)	1,047.7	LT Debt/Total Cap.:	61.8%
Avg. Daily Vol.:	1,080,690	ROE:	18%
S&P 500:	1,151.52	3-5 Yr. Est. Grth. Rate:	25%
Float: (MM)	34.0	CY 2005 Est. P/E-to-Grth.:	1.6x
Div./Yield:	$0.00/0.0%	Last Reporting Date:	4/26/2005 *After Close*

Key Points

- **Lowering estimates to reflect Velac push out.** 2005 EPS from $0.80 to $0.69, 2006 EPS from $1.18 to $0.97. Our new model reflects Q3 2006 Velac launch, although this is a preliminary estimate at best. Q2 2005 EPS from $0.12 to $0.08 to reflect higher operating costs.
- **Less certainty in Velac timing.** Communications from FDA regarding the Velac NDA may be suggestive of safety concerns. CNCT expects to submit additional information shortly. Velac is CNCT's proprietary clindamycin/tretinoin gel for the treatment of acne.
- **FDA questions preclinical results.** There was a positive response to Velac in a transgenic mouse model, which could raise toxicology issues. Given the Agency's current sensitivity to safety, this could temporarily delay the PDUFA action date (June 25) on Velac, in our view.
- **We expect CNCT shares to be under pressure.** Velac is widely considered by investors to be a major growth driver for CNCT in the near-to-intermediate term. Given the current uncertainty, CNCT shares could come under pressure. In addition, this could compress its headstart, if any, against Clin-RA.

Valuation Range: $22 to $24

Our valuation range is based on a P/E multiple of 23.0-25.0x our 2006 EPS estimate of $0.97. Risks to the stock trading at our valuation range include a regulatory setback for Velac, deceleration in Evoclin, and earlier than expected generic competition for Soriatane.

Michael Tong
(212) 891-5067
michael.tong@wachovia.com
Victor Lau
(212) 891-5035
victor.lau@wachovia.com
Samuel Martin
(212) 891-5097
samuel.martin@wachovia.com

Please see page 6 for rating definitions, important disclosures and required analyst certifications.

Investment Thesis
We believe CNCT's proprietary foam technology and 4:2:1 business model could provide consistent new product flow. However, the shares appear fairly priced relative to CNCT's near-term prospects, in our view.

Company Description
Connetics Corp. is a specialty pharmaceutical company focusing exclusively on the treatment of dermatological conditions. The company promotes its products directly to dermatologists through its 125-person sales force. CNCT outsources manufacturing and distributes through wholesalers.

Management's comments raised concerns regarding Velac approval timing, in our view. CNCT indicated that in the past several weeks, it received communications from FDA regarding the Velac NDA. The communication involves a pre-clinical study in which there was a positive response to Velac in a transgenic mouse model, which could suggest safety concerns. CNCT indicated that it is continuing discussions with FDA on this issue, and expects to submit additional information shortly. Velac is CNCT's proprietary clindamycin/tretinoin gel for the treatment of acne. It is pending approval at FDA, with an action date of June 25, 2005.

In our opinion, FDA action by the June 25 PDUFA date appears unlikely. Given CNCT management's expectation of providing additional information to the FDA over the next several weeks, it leaves very little time for FDA to process the information and make a decision by June 25. Therefore, we believe FDA will likely seek an extension to the PDUFA action date, possibly by three months.

Is there a risk to Velac's approvability? We do not have sufficient information at this point to assess the approvability of Velac. The major risk, in our view, relates to safety.

The factors that are in favor of Velac's approvability include:

- The active ingredients (clindamycin and tretinoin) are FDA-approved
- The issue relates to a *preclinical* model, and there has been no evidence of severe adverse events in *human clinical* studies

On the other hand, the factors that are not in favor include:

- Safety is a major concern to FDA, as there have been several high-profile drug safety issues (e.g. COX-2 inhibitors, Tysabri)
- Velac is being developed for the treatment of acne, not exactly the most pressing need for a product with potential safety issues.

Ultimately, we believe Velac is approvable, on the strength of its Phase III data, in terms of efficacy and lack of serious adverse events. However, a delay in FDA action is highly probable, as we mentioned before. Therefore, we have adjusted our model to reflect the delay, although management maintains its prior revenue and EPS guidance (which are $196-$205 million and $0.88-$0.92, respectively). Management's guidance reflects Q3 2005 launch of Velac.

We believe the stock could trade at a valuation range of $22-$24 over the next 6-12 months. Our valuation range is based on a P/E multiple of 23.0x-25.0x our calendar EPS estimate of $0.97. CNCT has undergone recent multiple expansion, primarily on expectation of rapid EPS growth and from perceived headstart in the combination acne gel market. Given the uncertainty in Velac, the shares may see near-term multiple contraction. Risks to the stock trading at our valuation range include significant regulatory setback in Velac, deceleration in Evoclin growth, and earlier than expected generic Soriatane competition.

Lowering 2005 EPS estimate to $0.69 from $0.80 to reflect removal of Velac revenue. We have lowered our FY 2005 revenue estimate to $184.8 million from $198.8 million and our EPS estimate to $0.69 from $0.80. The downward revision in EPS reflects removal of $18.0 million in

Velac revenue, partially offset by an increase in sales of the other brands. Absent the Velac launch, CNCT should be able to focus more sales and marketing resources on its other brands.

Exhibit 1. Wachovia 2005 Product Revenue Estimates

Product ($MM)	New Estimate	Previous Estimate
Luxiq	25.7	24.8
OLUX	70.6	71.3
Soriatane	66.5	62.8
Evoclin	19.8	19.6
Velac	0.0	18.0
Other	2.2	2.3
Total	184.8	198.8

Source: Wachovia Capital Markets, LLC estimates

We are also lowering our Q2 EPS estimate to 0.08 from 0.12 to reflect higher operating expenses. While we have slightly increased our Q2 revenue assumption to $46.1 million from $44.0 million, these increased revenues are more than offset by higher operating expenses in Q2. CNCT expects to incur significant expenses in Q2 2005. Management guided to operating expenses of $34 to $36 million in Q2 driven by Evoclin marketing expenses, Velac pre-marketing activities, and higher administrative & co-promotion expenses related to ramping up the Ventiv agreement. For these reasons, we have increased our SG&A assumption to $27.0 million from $22.5 million.

Management's revenue and EPS guidance for Q2 2005 were $45-$47 million and $0.06-$0.08, respectively.

Lowering FY2006 EPS estimate to $0.97 from $1.18 to reflect H2 2006 launch of Velac. We have lowered our FY2006 revenue estimate to $230.9 million from $258.6 million. The decreased revenue reflects lowering our FY2006 Velac revenue to $13.2 million from $46.2 million to reflect a 2H 20006 launch. However, we acknowledge that any projection of Velac approval timing is conjecture at best, owing to the limited information we have been presented with. On the expense side, we have lowered FY2006 operating expenses to $140.7 million from $146.0 million to reflect the later Velac launch. We have also reduced our tax rate to 20% from 25% as lower 2005 and 2006 profitability would deplete CNCT's deferred tax asset at a slower rate.

We note that our FY2006 EPS and revenue estimates also assume generic Soriatane competition beginning in Q1 2006. In the even that a generic version of Soriatane does not materialize, our EPS estimate would increase to $1.47 on revenue of $259.5 million.

CNCT delivered $0.01 EPS upside, although revenue was lower than consensus. Reported Q1 2005 EPS were $0.03 on revenue of $42.4 million. Our corresponding estimates were $0.02 and $44.3 million, and consensus estimates were $0.02 and $43.2 million. Revenue growth of 69.6% yr/yr was driven by the addition of Soriatane and Evoclin, along with continued growth of OLUX and Luxiq. Although revenue was below our expectation, CNCT was able to more than offset this with higher gross margin and lower operating expenses. Gross margin of 91.1% was 110bps above our estimate. Operating expenses were $1.6 million below our estimate ($33.4MM A vs. $35.0MM E). At $5.8 million, R&D was $1.2 million below our expectation and SG&A of $27.6 million was $0.4 million below our estimate.

Exhibit 1. Q1 2005 Results vs. Wachovia's Prior Estimates

	Reported Actual	Wachovia Estimate	Actual vs. Estimate
Revenue ($MM)	42.4	44.3	(1.9)
yr/yr growth	69.6%	77.3%	(7.7%)
Gross Margin	91.1%	90.0%	1.1%
SG&A ($MM)	27.6	28.0	(0.4)
yr/yr growth	82.7%	85.3%	(2.6%)
R&D ($MM)	5.8	7.0	(1.2)
yr/yr growth	29.8%	57.6%	(27.9%)
Operating Income ($MM)	1.5	0.9	0.6
yr/yr growth	(42.2%)	(66.4%)	24.3%
Operating Margin ($MM)	3.5%	2.0%	1.6%
Tax Rate	9.2%	10.0%	(0.8%)
Net Income ($MM)	1.0	0.7	0.4
yr/yr growth	(44.4%)	(63.3%)	18.9%
Net Margin ($MM)	2.5%	1.6%	0.9%
EPS	0.03	0.02	.01
yr/yr growth	(47.5%)	(65.5%)	18.0%

Source: Company Reports and Wachovia Capital Markets, LLC estimates

Year-over-year revenue growth in-line with expectations. Q1 OLUX and Luxiq combined revenues grew 8.1% yr/yr with OLUX increasing 9.7% and Luxiq 3.8%. Soriatane revenue came in at $17.6 million, $0.5 million below our expectation. Management declined to break out US and international Soriatane sales, but did mention that Soriatane international sales were in line with an annual run rate of ~$12 million.

Exhibit 3. Q1 2005 Revenue vs. Wachovia's Prior Estimates

Product ($MM)	Reported Actual	Wachovia Estimate	Actual vs. Estimate
Luxiq	5.7	6.3	(0.6)
yr/yr growth	3.8%	15.0%	(11.2%)
OLUX	15.8	16.7	(0.9)
yr/yr growth	9.7%	16.1%	(6.4%)
Soriatane	17.6	18.1	(0.5)
yr/yr growth[1]	N/A	N/A	N/A
Evoclin	3.1	2.9	0.2
yr/yr growth	N/A	N/A	N/A
Other	0.2	0.3	(0.1)
yr/yr growth	(87.9%)	(79.9%)	(8.0%)

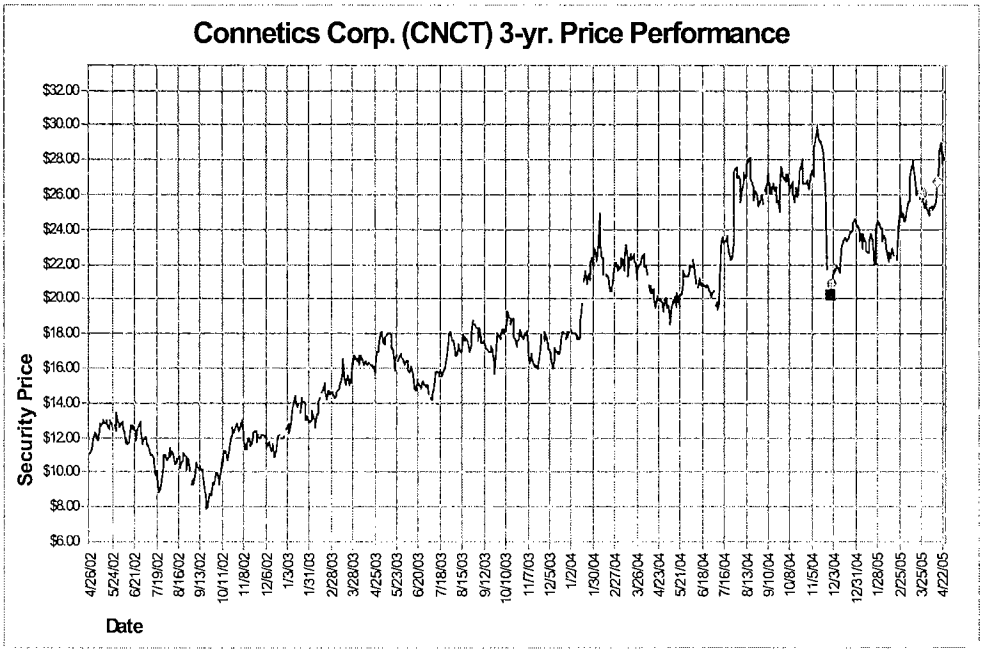
1. Soriatane acquired Q1 2004, only partial quarter sales.
Source: Company Reports and Wachovia Capital Markets, LLC estimates

CONNETICS CORPORATION
EARNINGS MODEL
($ million except per share data)

	2004A					2005E					2006E
	Q1	Q2	Q3	Q4	Year	Q1	Q2	Q3	Q4	Year	Year
Revenue											
Product sales	23.6	38.0	37.0	43.5	**142.1**	42.2	45.8	46.9	47.7	**182.6**	**218.5**
Royalty	1.4	0.2	0.1	0.3	**1.9**	0.2	0.2	0.5	1.0	**1.9**	**12.0**
License, contract, and other	0.1	0.1	0.3	0.0	**0.4**	0.0	0.1	0.1	0.1	**0.3**	**0.4**
Total revenue	25.0	38.3	37.3	43.8	**144.4**	42.4	46.1	47.5	48.8	**184.8**	**230.9**
Cost of product revenue	1.6	3.6	3.1	4.4	**12.7**	3.8	4.4	4.5	4.9	**17.5**	**23.1**
Gross profit	23.4	34.7	34.3	39.3	**131.7**	38.6	41.8	43.0	43.9	**167.3**	**207.8**
Operating costs and expenses											
R&D	4.4	5.1	6.2	5.7	**21.4**	5.8	7.0	7.5	6.5	**26.8**	**28.4**
SG&A	15.1	17.5	17.0	23.2	**72.8**	27.6	27.0	19.0	20.0	**93.6**	**112.3**
Acquired in-process R&D/milestone	0.0	0.0	3.5	0.0	**3.5**	0.0	0.0	0.0	0.0	**0.0**	**0.0**
Amortization	1.3	3.4	3.4	3.8	**11.8**	3.7	3.8	4.1	4.1	**15.8**	**16.3**
Loss on program termination	0.0	0.0	0.0	0.0	**0.0**	0.0	0.0	0.0	0.0	**0.0**	**0.0**
Total operating expenses	20.8	26.0	30.1	32.7	**109.5**	37.1	37.8	30.6	30.6	**136.2**	**157.0**
Operating income	2.6	8.7	4.2	6.7	**22.2**	1.5	4.0	12.4	13.3	**31.1**	**50.8**
Other income											
Interest income	0.3	0.2	0.3	0.0	**0.8**	0.0	0.0	0.3	0.3	**0.6**	**1.0**
Gain on sale of investment	0.0	0.0	0.0	0.0	**0.0**	0.0	0.0	0.0	0.0	**0.0**	**0.0**
Interest expense	(0.9)	(0.7)	(0.7)	(0.2)	**(2.5)**	(0.4)	(0.5)	(1.0)	(1.0)	**(2.9)**	**(4.0)**
Gain on sale of FX forward contract	0.0	0.0	0.0	0.0	**0.0**	0.0	0.0	0.0	0.0	**0.0**	**0.0**
Gain on sale of Riadura line	0.0	0.0	0.0	0.0	**0.0**	0.0	0.0	0.0	0.0	**0.0**	**0.0**
Other income (expense), net	0.1	(0.1)	0.0	0.0	**0.0**	0.0	0.0	0.0	0.0	**0.0**	**0.0**
Total other income	(0.5)	(0.6)	(0.4)	(0.2)	**(1.7)**	(0.4)	(0.5)	(0.7)	(0.7)	**(2.3)**	**(3.0)**
Pretax income	2.1	8.1	3.8	6.4	**20.5**	1.1	3.5	11.7	12.6	**28.8**	**47.8**
Income taxes	0.2	0.6	0.1	0.5	**1.5**	0.1	0.3	1.2	1.3	**2.9**	**9.6**
Net income	1.9	7.5	3.7	6.0	**19.0**	1.0	3.1	10.5	11.3	**26.0**	**38.2**
Shares outstanding (diluted)	35.9	37.4	38.1	38.2	**37.4**	38.0	36.7	36.7	36.7	**37.0**	
Shares outstanding (convert)	40.1	41.6	42.3	42.4	**42.4**	42.1	40.8	40.8	40.8	**41.1**	**41.0**
Earnings per share data:											
Reported EPS	$0.05	$0.19	$0.10	$0.16	**$0.51**	$0.03	$0.08	$0.27	$0.29	**$0.69**	**$0.97**
Adjustment	0.00	0.00	0.00	0.00	**0.00**	0.00	0.00	0.00	0.00	**0.00**	**0.00**
Adjusted EPS	$0.05	$0.19	$0.10	$0.16	**$0.51**	$0.03	$0.08	$0.27	$0.29	**$0.69**	**$0.97**
Ratio Analysis											
Gross margin	93.7%	90.6%	91.8%	89.9%	**91.2%**	91.1%	90.5%	90.5%	90.0%	**90.5%**	**90.0%**
Operating margin	10.4%	22.8%	11.3%	15.2%	**15.4%**	3.5%	8.6%	26.1%	27.2%	**16.8%**	**22.0%**
Net margin	7.5%	19.5%	9.9%	13.7%	**13.2%**	2.5%	6.7%	22.1%	23.2%	**14.1%**	**16.6%**
R&D/total revenue	17.8%	13.3%	16.5%	13.0%	**14.8%**	13.6%	15.2%	15.8%	13.3%	**14.5%**	**12.3%**
SG&A/total revenue	60.5%	45.7%	45.5%	53.1%	**50.4%**	65.1%	58.5%	40.0%	41.0%	**50.7%**	**48.7%**
Tax rate	11.5%	8.0%	3.8%	7.1%	**7.3%**	9.2%	10.0%	10.0%	10.0%	**10.0%**	**20.0%**
Growth Analysis (year-over-year)											
Revenue	63.2%	91.6%	89.4%	115.2%	**91.6%**	69.6%	20.6%	27.3%	11.4%	**28.0%**	**24.9%**
SG&A	38.6%	64.9%	70.6%	120.0%	**73.4%**	82.7%	54.6%	11.9%	(14.0%)	**28.6%**	**20.0%**
R&D	(48.5%)	(40.9%)	(0.5%)	(12.7%)	**(28.9%)**	29.8%	37.4%	21.4%	14.3%	**25.0%**	**6.0%**
Operating income	NM	NM	116.0%	276.2%	**NM**	(42.2%)	(54.6%)	194.1%	99.4%	**40.3%**	**63.3%**
Pretax income	NM	NM	135.7%	326.0%	**NM**	(45.8%)	(57.4%)	204.4%	94.8%	**40.7%**	**65.7%**
Net income	NM	NM	128.7%	265.7%	**NM**	(44.4%)	(58.3%)	184.7%	88.7%	**36.6%**	**47.2%**
EPS (adjusted)	NM	NM	101.9%	222.8%	**NM**	(47.5%)	(55.6%)	180.0%	85.5%	**35.3%**	**41.5%**

Source: Company reports and Wachovia Capital Markets, LLC estimates

Required Disclosures



	Date	Close Price ($)	Rating Code	Target Price ($)	Val. Rng. Low	Val. Rng. High
■	11/30/2004	Tong				
○	12/1/2004	20.91	2	NE	21.00	23.00
○	3/28/2005	26.10	2	NE	25.00	27.00
○	4/15/2005	26.80	2	NE	26.00	29.00

Source: Wachovia Capital Markets, LLC estimates and Bridge data

Beginning 01/04/2003 stock valuation range replaces target price

Symbol Key

◆ Rating Scale Conversion
○ Rating, Target Price and/or Val. Rnge. Chnge.
▼ Rating Downgrade
▲ Rating Upgrade
■ Analyst Change
Split Adjustment

Rating Code Key

1	Outperform	SR	Suspended
2	Market Perform	NR	Not Rated
3	Underperform	NE	Not Estimate

Additional Information Available Upon Request

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Risks to the stock trading at our valuation range include a regulatory setback for Velac, deceleration in Evoclin, and earlier than expected generic competition for Soriatane.

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1 = Outperform: The stock appears attractively valued, and we believe the stock's total return will exceed that of the market over the next 12 months. BUY

2 = Market Perform: The stock appears appropriately valued, and we believe the stock's total return will be in line with the market over the next 12 months. HOLD

3 = Underperform: The stock appears overvalued, and we believe the stock's total return will be below the market over the next 12 months. SELL

As of: April 26, 2005

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54% of companies covered by Wachovia Equity Research are rated Market Perform.
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Wachovia has provided investment banking services for 25% of its Underperform-rated companies.

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SECURITIES: NOT FDIC-INSURED/NOT BANK-GUARANTEED/MAY LOSE VALUE

EXHIBIT 46

Specialty Pharmaceuticals **Rating Change – April 27, 2005**

David H. Windley, CFA, CPA (615) 963-8313 dwindley@jefco.com Himanshu Rastogi, Ph.D. (615) 963-8339 hrastogi@jefco.com

Connetics Corporation

NASDAQ: CNCT – $27.57

Rating: Hold

52-Week Range	$30.41 – $17.95	FY Dec	2004	2005E	2006E
Shares Out (MM)	38	1Q	$0.05	$0.03A	--
Float (MM)	34	2Q	0.19	0.06E	--
Insider Ownership	11%	3Q	0.10	0.24E	--
Institutional Ownership	110%	4Q	0.17	0.34E	--
Avg. Daily Vol (000)	855	EPS	$0.51	$0.68E	$1.26E
Equity Market Cap (MM)	$1,048	P/E	54x	40.5x	21.9x
Total Enterprise Value (MM)	$1,104	Revenue	$144	$188	$247
Long-term Debt (MM)	$290	EBITDA	$39	$44	$77
Price Target	$25	EV/EBITDA	28.3x	25.1x	14.3x
		($MM, except per share data)			

Velac Approval Will Most Likely Get Delayed

We are downgrading the shares of Connetics Corporation to a **Hold** (from a Buy) and lowering our 12-month price target to **$25** (from $31.50). Management disclosed during the earnings call yesterday that the FDA has sought more information on preclinical studies conducted on Velac. We continue to believe that Velac should get approved, but a positive FDA decision by the 10-month PDUFA date looks difficult at this point, in our opinion. Connetics is a dermatology-focused specialty pharmaceutical company. Its portfolio and pipeline target two of the largest markets within dermatology, acne and psoriasis.

Rationale for the downgrade

Under the general rules of thumb that future outlook is more important than the reported results and uncertainty never sits well, the lower 2Q guidance and revelations of an 11th hour FDA safety inquiry overwhelm the modest 1Q upside surprise, in our view. We considered several factors in ultimately deciding to downgrade the stock.

1. Notwithstanding any potential Velac delays, Connetics' EPS are more severely back-end loaded than we, and the consensus, had anticipated. To us, this signals an even greater dependence on a timely Velac launch (early 3Q).
2. We expect Velac to get approved, but not in June. Visibility on the exact timing is very low. We moved our assumption back six months (to January), which results in $0.10 - $0.15 of 2005 sensitivity and $0.18 - $0.22 of 2006 sensitivity. We did adjust expenses down somewhat in 2006.
3. Based on our expectation of eventual approval, we continue to forecast attractive, though lower growth over the next several years. We think this growth outlook and management's effort to continually build pipeline provide some downside protection to the stock. This should also warrant a premium multiple to the specialty pharma group, which trades at 16x 2006, though that will likely be ignored in Wednesday's trading, we believe.
4. Even then, a 20x (a 25% premium) multiple on our $1.26 estimate for 2006 produces a $25 price target, 10% below last night's close but above the level's in after hours trading.
5. Anticipating the gap down on the open Wednesday, this stock is a Hold, not an Underperform/Sell. The stock should settle around $24-$25, we believe. To get more constructive, we will look for better visibility on the transgenic mouse tumor issue, rapid acceleration in scripts in the Ventiv contract, and/or a cleaner (read lack of generics) outlook for Soriatane.

The issue facing Connetics on Velac is not unknown

Here is an excerpt from the FDA approved label for the acne treatment BenzaClin topical gel, a combination product consisting of clindamycin (one of Velac's ingredients) and benzoyl peroxide. The quote is taken from the section on Carcinogenesis, Mutagenesis, Impairment of Fertility on page 5 of the label.

"Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced skin tumors in transgenic Tg.AC mice in a study using 20 weeks of topical treatment."

In preclinical studies, Velac was tested in the same mice specimen as underlined above. In our off-line conversation, management revealed that only one mouse displayed a similar response as the one mentioned in the quote above. Management evaluated this data while Velac was under development and decided that the response does not have clinical relevance. The fact that BenzaClin (and a similar product, Duac), are widely prescribed, lends support management's stand, in our opinion. Connetics expects to submit a response to the FDA in the coming weeks, before the 10-month PDUFA date, and management is hopeful that Velac will receive a timely approval. Hence, it is not revising 2005 guidance. We are taking a more conservative position given the heightened concern around drug safety, in general, at the FDA. The PDUFA date is only two months away, and this may not be sufficient to resolve the issue to FDA's satisfaction. Hence, we are assuming that the Agency will require a typical three-month extension for completing its review.

Quarter's results versus our forecast

Connetics reported EPS of $0.03 for the first quarter. Our forecast was $0.01. Higher gross margin and lower R&D expenses versus our forecast led to the EPS upside. Product revenue was $42.2 million, in line with our forecast ($41.9 million). While sales of OLUX and Luxiq were lower than we had estimated, Soriatane and Evoclin beat our forecast. OLUX (clobetasol) sales were $15.8 million, down $0.5 million from 4Q04. Total prescriptions declined by 1,600 in that period. The combined volume of all clobetasol products (branded and generic) was flat sequentially. Luxiq sales were $5.7 million, also $0.5 million lower than the fourth quarter sales. Total Luxiq prescriptions were comparable to last quarter's. Soriatane sales were $17.6 million, a million higher than our forecast. Total prescriptions were essentially the same as in 4Q04. Evoclin sales were $3.1 million, $0.7 million higher than our forecast. Nearly 30,000 prescriptions were dispensed in 1Q05, Evoclin's first full quarter on the market.

Gross margin was 91.1%, 110 basis points higher than we had estimated, and 130 basis points higher than the gross margin in 4Q04. Product mix was responsible for the observed movement in gross margin. SG&A expenses were in line with our estimate, but lower than what management said it had budgeted. R&D expenses were a million lower than our forecast. Operating expenses are expected to increase in the second quarter. Connetics is running Phase III trials for two products, Desilux and Primolux. These will cause R&D expenses to grow sequentially. SG&A expenses are forecast to be much higher in the first half of the year due to costs associated with the ramp of Ventiv contract (VTIV, Buy, $21.61), continued investment in Evoclin, and pre-launch expenses associated with Velac.

Guidance and Estimates

Management expects sales growth in all four marketed products in the balance of the year. Based on the positive experience with UCB Pharma, management believes that the contract sales force hired from Ventiv will help rejuvenate prescription growth in OLUX and Luxiq. The EPS guidance for 2Q05 was set well below the current consensus ($0.18). For the second quarter, our revenue forecast ($45 million) is at the low end of management's guidance ($45-$47 million). However, the guidance for SG&A expense was much higher than we had previously assumed. Consequently, we are lowering our second quarter EPS estimate from $0.23 to $0.06. SG&A expenses are heavily front-end loaded. SG&A expenses are expected to decline after 2Q05, and thus 2H05 EPS is projected to be significantly higher (~$0.80, assuming mid-point of guidance).

We have pushed Velac in our model to the first quarter of 2006. This has lowered our 2005 revenue forecast by about $6 million. Operating expenses are $5 million higher in our revised forecast. These changes reduce the 2005 EPS from $0.84 to $0.68. The delayed introduction of Velac lowers our 2006 revenue forecast by about $20 million. Our 2006 EPS goes to $1.26 from $1.48. This still represents a very healthy 85% year-over-year EPS growth. We expect growth to remain strong in 2007 as Velac ramps and at least two new products, Desilux and Primolux, start contributing. Hence, we continue to value CNCT at

a premium to the group. Our $25 price target is based on 20x our 2006 estimate. The stock was trading around $23 in the aftermarket yesterday, within 10% of our price target. We are lowering CNCT to a Hold.

Table 1: Product Sales Forecast (2005-06)

	2005E			2006E		
Product	**Volume**	**Sales ($million)**	**Percent Contribution**	**Volume**	**Sales ($million)**	**Percent Contribution**
OLUX	490	70	37%	536	79	32%
Luxiq	292	25	14%	302	27	11%
Soriatane (U.S.)	132	59	32%	138	63	26%
Soriatane (ex-U.S.)		11	6%		11	4%
Evoclin	236	19	10%	445	38	16%
Velac	0	2	1%	202	27	11%
Product Revenue		**187**			**246**	

Source: Jefferies & Company, Inc

Table 2: Earnings Model ($ thousands, except per share data)

FY December	2004					2005E					2006E
	Q1	Q2	Q3	Q4	2004	Q1	Q2	Q3	Q4	2005	2006
Product Revenue	23,566	37,999	36,999	43,495	142,059	42,190	44,680	47,629	52,878	187,377	246,463
Contract and royalty	1,416	254	345	281	2,296	181	200	200	200	781	800
Total revenue	24,982	38,253	37,344	43,776	144,355	42,371	44,880	47,829	53,078	188,158	247,263
Cost of products sold	1,568	3,578	3,067	4,443	12,656	3,766	4,212	4,490	4,984	17,452	26,417
R&D	4,286	4,957	6,038	5,687	20,968	5,763	6,732	5,979	6,104	24,578	34,678
SG&A	15,072	17,239	16,789	23,245	72,345	27,601	27,826	23,436	23,354	102,217	108,796
Total operating expenses	20,926	25,774	25,894	33,375	105,969	37,130	38,770	33,904	34,443	144,246	169,891
EBITDA	4,056	12,479	11,450	10,401	38,386	5,241	6,111	13,924	18,635	43,911	77,372
D&A	1,648	3,767	3,738	3,750	12,903	3,742	3,857	4,016	4,217	15,832	17,092
EBIT	2,408	8,712	7,712	6,651	25,483	1,499	2,254	9,909	14,418	28,080	60,281
Interest income (expense)	(292)	(608)	(373)	(202)	(1,475)	(353)	486	529	597	1,259	3,108
Other/charges	-	-	(3,500)	-	(3,500)	-	-	-	-	-	-
Pretax Income	2,116	8,104	3,839	6,449	20,508	1,146	2,740	10,437	15,015	29,338	63,388
Taxes	243	647	144	459	1,493	105	274	1,044	1,502	2,924	14,262
Net Income	1,873	7,457	3,695	5,990	19,015	1,041	2,466	9,394	13,514	26,414	49,126
EPS	**$ 0.05**	**$ 0.19**	**$ 0.10**	**$ 0.16**	**$ 0.51**	**$ 0.03**	**$ 0.06**	**$ 0.24**	**$ 0.34**	**$ 0.68**	**$ 1.26**
Weighted Shares O/S	35,887	41,627	38,064	38,172	37,433	38,014	38,314	38,814	39,314	38,614	38,864
Common Size:											
Product Revenue	94.3%	99.3%	99.1%	99.4%	98.4%	99.6%	99.6%	99.6%	99.6%	99.6%	99.7%
Contract and royalty	5.7%	0.7%	0.9%	0.6%	1.6%	0.4%	0.4%	0.4%	0.4%	0.4%	0.3%
Total revenue	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Direct costs (Product)	6.7%	9.4%	8.3%	10.2%	8.9%	8.9%	9.4%	9.4%	9.4%	9.3%	10.7%
Gross margin	93.3%	90.6%	91.7%	89.8%	91.1%	91.1%	90.6%	90.6%	90.6%	90.7%	89.3%
R&D	17.2%	13.0%	16.2%	13.0%	14.5%	13.6%	15.0%	12.5%	11.5%	13.1%	14.0%
SG&A	60.3%	45.1%	45.0%	53.1%	50.1%	65.1%	62.0%	49.0%	44.0%	54.3%	44.0%
Total operating expenses	83.8%	67.4%	69.3%	76.2%	73.4%	87.6%	86.4%	70.9%	64.9%	76.7%	68.7%
EBITDA Margin	16.2%	32.6%	30.7%	23.8%	26.6%	12.4%	13.6%	29.1%	35.1%	23.3%	31.3%
D&A	6.6%	9.8%	10.0%	8.6%	8.9%	8.8%	8.6%	8.4%	7.2%	8.4%	6.9%
EBIT Margin	9.6%	22.8%	20.7%	15.2%	17.7%	3.5%	5.0%	20.7%	27.2%	14.9%	24.4%
Interest income (expense)	-1.2%	-1.6%	-1.0%	-0.5%	-1.0%	-0.8%	1.1%	1.1%	1.1%	0.7%	1.3%
Other/charges	0.0%	0.0%	-9.4%	0.0%	-2.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Pretax Income	8.5%	21.2%	10.3%	14.7%	14.2%	2.7%	6.1%	21.8%	28.3%	15.6%	25.6%
Taxes	11.5%	8.0%	3.8%	7.1%	7.3%	9.2%	10.0%	10.0%	10.0%	10.0%	22.5%
Net Income	7.5%	19.5%	9.9%	13.7%	13.2%	2.5%	5.5%	19.6%	25.5%	14.0%	19.9%

Source: Company SEC Filings, Jefferies & Company, Inc.

We, David H. Windley, CFA, CPA and Himanshu Rastogi, certify that all of the views expressed in this research report accurately reflect our personal views about the subject security(ies) and subject company(ies). We also certify that no part of our compensation was, is, or will be, directly or indirectly, related to the specific recommendations or views expressed in this research report.

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Jefferies makes a market in Connetics Corp. and VENTIV HEALTH INC.

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	% Companies Covered	% Banking Clients
Buy	51	19
Hold/Neutral	43	12
Underperform/Sell	6	n/a

Price Chart(s)

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The company that is the focus of this report has been covered by Jefferies for less than one year. Therefore, no price chart is provided.

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EXHIBIT 47

Summer Street
RESEARCH PARTNERS

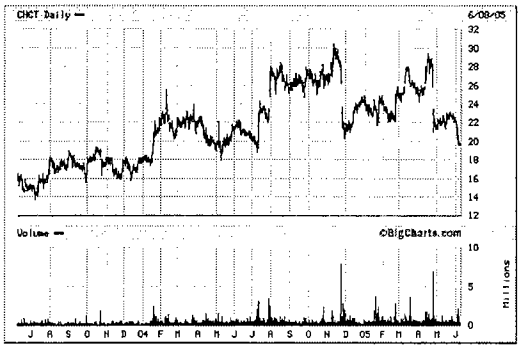
One Beacon Street
34th Floor
Boston, MA 02108
617-532-6400

Connetics – Outlook for Velac PDUFA Date

June 9, 2005

Recommendation: NEUTRAL

Jon Stephenson, CFA jons@summersp.com



Source: Bigcharts.com

Stock Data (CNCT)

Price	$19.66
52-wk high:	$30.41
52-wk low:	$18.80
Shares out:	35.9MM
Float:	33.8MM
Shares short:	5.4MM
Avg vol (10-day):	0.9MM

Valuation Metrics

Market cap:	$706.4MM
Enterprise value:	$762.7MM
Book value/share:	$2.66

Financial Highlights (Mar:05)

Cash/equivalents:	$233.7MM
Debt:	$290.0MM
Book value:	$95.5MM
Cash Flow (TTM):	$47.9MM

- The PDUFA date for Connetics' Velac (tretinoin-clindamycin gel, for the treatment of acne) is rapidly approaching (6/25/05).
- In our opinion, a delay in the approval/launch of Velac of approximately one quarter is the most likely outcome (60% probability), with a 12-18 month delay having a 20% probability and an approval on the 6/25/05 PDUFA date having a 20% probability.
- We continue to believe that the market for retinoid-containing combinations will be more competitive than many analysts forecast. Our model still assumes an approval/launch of Medicis' (NYSE:MRX-$29.04-Neutral) Clin-RA in H2:05. We have also learned that Galderma completed a late stage clinical trial of another acne combination, Differin and benzoyl peroxide. This is an added risk that has not been reflected in our model.
- Additionally, Connetics announced yesterday that it plans to initiate a confirmatory trial of Extina (ketoconazole foam). This trial will have increased power to detect the difference between the drug and placebo vehicle when compared to the previous trial. We have assumed a 2H:07 launch in our model.
- We believe that if a minor delay (one quarter) in the Velac approval/launch occurs, the stock will trade up modestly. In our opinion, a significant delay (12-18 months) would results in a mid-teens price and an approval could drive the stock into the low/mid $20's. Therefore, the current price may present a near-term buying opportunity. However, we continue to rate Connetics Neutral as we believe investors are overly bullish on Velac's potential.

Investment Thesis

Connetics business strategy revolves around the development of topical dermatology products, utilizing its foam and gel formulation. This is a highly competitive market and the timing of competition is difficult to project. Additionally, the company's revenues and EPS are significantly leveraged to Soriatane, an oral product for the treatment of severe psoriasis. We rate shares of Connetics NEUTRAL due to the risk of generic soriatane and conservative estimates for Velac market potential.

VELAC – CARCINOGENICITY SIGNAL

On April 26, Connetics announced that the FDA asked questions about the company's preclinical toxicology work in its NDA submission of Velac, a topical gel combining tretinoin and clindamycin. We understand, the company saw a carcinogenic signal (increased incidence of papillomas on the skin) when assessing the combination of clindamycin plus the vehicle in a transgenic mouse model. In an effort to gain a greater understanding of the issues surrounding transgenic mouse models, we spoke with some toxicologists who have first hand experience with the FDA and/or preclinical toxicology studies. Our sources found this preclinical signal somewhat perplexing given that clindamycin has such an extensive history of use and is not known to be carcinogenic. That being said, it is important to note that in a hairless mouse model in which the animals were exposed to simulated sunlight, Galderma's Clindagel exhibited a statistically significant decrease in the median time to tumor onset.

We reviewed the potential components of the Velac vehicle (outlined in patent # 5,690,923) with our consultants and they noted that none of the potential components were known to induce a carcinogenic response. However, we cannot rule out the possibility that this could have occurred or that any of the components has acted synergistically with either clindamycin or another component of the vehicle.

Additionally, our consultants indicated that it is theoretically possible for spontaneous tumors to present in a transgenic mouse model. For example, this could occur if the mice were to scratch themselves extensively in a given region and they were prone to dermatitis. Additionally, if these mice were subjected to infection, it could further increase the chances of tumor formation unrelated to the product. If the tumors seen in the preclinical trials were unrelated to the drug, Connetics would be required to submit evidence that there were other issues predisposing these mice to increased risk of tumor formation.

We have received mixed opinions from our toxicology experts as to whether or not the FDA is likely to require that Connetics perform additional preclinical trials with Velac before receiving approval. One consultant believed that when an unusual signal such as that seen with Velac occurs, the FDA would require additional preclinical work in order a) to determine the cause of this result or b) to verify that the signal was spurious. Another toxicology expert with whom we spoke believed that the product would likely be approved with a post-marketing commitment and a carcinogenicity warning, in light of the known safety of the two active ingredients.

We see three possible scenarios regarding the timing of Velac. First, the FDA could choose to approve the product on the PDUFA date (6/25/05). In this scenario, the product's label would include a warning pertaining to a carcinogenic signal in the transgenic mouse model. Our dermatology consultants believe this would have a small impact on the marketability of the product. Secondly, the agency could choose to extend the PDUFA date. We understand that the company has submitted a response to the FDA's questions. We suspect that this response consists only of consultant's opinion regarding the carcinogenicity signal since the company has not had time to generate additional preclinical data on the product. It is also possible that the company has (or could) submitted a new proposed label. The FDA could utilize either as a reason to extend the PDUFA date on Velac. We believe this would result in a delay of a few months and would imply a Q4:05 launch of Velac. Lastly, it is possible that the agency could ask for additional preclinical data. We believe if the agency chooses to pursue this route, it would likely lead to a 12-18 month delay in the product's launch, implying a H2:06 launch.

Overall, we believe some delay in the approval of Velac is likely (>90%), with a short delay the most likely outcome (60%) and a long delay being less likely (20%). We believe that the FDA will likely view any additional submissions as a reason for delay, but that the product will likely have a short delay due to the fact that both chemical entities are broadly used today. In this scenario, the impact of a modest delay to Velac hinges upon the timelines for similar products looming on the horizon. If other products such as

Medicis' Clin-RA enter the market in H2:05, the impact of even a short delay for Velac would be magnified. It should be noted that we have already assumed a H2:05 launch of Clin-RA in our Connetics projections.

CLIN-RA – STILL ON THE HORIZON

When we initiated on Connetics with a Neutral rating on 3/8/05, we pointed out that Medicis also had a tretinoin-clindamycin combination product nearing market. There has been persistent speculation that this product was significantly delayed due to either a) an approvable letter requiring additional studies or b) problems with the results of its phase III program prior to submission. We continue to believe that a H2:05 approval of this product is very possible (>50% probability).

Additionally, we believe that it is possible that Clin-RA has been delayed due to issues similar to those raised by the agency regarding the Velac NDA. If this is the case, one of two scenarios will play out: 1) Both products will come to market in the near term and they fight for share or 2) neither product comes to market any time soon as the FDA requests additional preclinical data. Either scenario would be a negative for Connetics relative to consensus expectations. The first scenario is reflected in our estimates.

Figure 1: Incremental EPS with 12-18 month Delay in Clin-RA

	2005	2006	2007	2008	2009
Currrent Projected Revenues	$188.0	$246.0	$283.8	$342.6	$400.7
Revenues	$6.0	$24.0	$30.0	$33.0	$35.5
COGS	($0.6)	($2.4)	($3.0)	($3.3)	($3.6)
Interest Income	$0.1	$0.3	$0.8	$1.4	$2.2
Pretax Impact	**$5.5**	**$21.9**	**$27.8**	**$31.1**	**$34.1**
Tax Expense	($1.9)	($7.7)	($9.7)	($10.9)	($11.9)
Net Income	**$3.6**	**$14.3**	**$18.1**	**$20.2**	**$22.2**
Incremental EPS	**$0.08**	**$0.33**	**$0.42**	**$0.46**	**$0.50**
Shares	**42.2**	**42.6**	**43.1**	**43.5**	**43.9**

ANOTHER COMBINATION PRODUCT COMING

As a result of our diligence we have also learned that Galderma is in late stage development on a combination of Differin (adapalene) and benzoyl peroxide. We believe that this product, if approved, would have a negative impact on the market opportunity for both Velac and Clin-RA. Bacterial resistance to benzoyl peroxide is not a possibility while it is a potential problem for clindamycin. Additionally, many clinicians prefer Differin's tolerability to that of tretinoin. Both issues would be effective detailing messages for Galderma when competing against Velac and/or Clin-RA. Connetics counter-detail message against a Differin-benzoyl peroxide product would likely focus on the potential bleaching (clothing, sheets, etc) that such a combination could cause due to the benzoyl peroxide.

A potential launch timeline for this product is difficult to pinpoint. However, if the company ran two successful parallel studies, it could theoretically be on the market in H2:06, assuming a filing in H2:05. Therefore, a potential approval of Differin-benzoyl peroxide could slow the growth rate of Velac in 2006 and beyond. We estimate that the product could negatively impact sales of Velac by 10-15%. Differin-BP is not currently in our Connetics assumptions and therefore represents an added risk to the stock.

REVENUE GROWTH OUTLOOK

Outside of the recently launched Evoclin (acne), end-market demand is slowing for Connetics current products. Year/year growth in prescriptions for Olux (non-scalp psoriasis) and Luxiq (scalp dermatoses) appears to have slowed to high single-digits over the last 6 weeks, from low-mid teens over the last several quarters. These two products account for 50% of Connetics total sales. We estimate that Olux & Luxiq combined will contribute $94mm to Connetics 2005 revenues. Meanwhile, year/year growth in prescriptions for Soriatane appears to approximate 4-5% in the most recent months. U.S. sales of Soriatane account for approximately 29-30% of Connetics total revenues. We estimate that U.S. sales of Soriatane will contribute approximately $50mm to 2005 revenues for the company. As we've previously highlighted, Soriatane has no Hatch-Waxman or patent protection and therefore potential competition from generics is always looming. There are currently two active Drug Master Files on record with the FDA. The timing of competition is uncertain since these potential generics would be approved under paragraph III of Hatch-Waxman.

If the Velac launch is delayed by 12-18 months, Connetics revenue growth will have to come predominantly from the launch of Evoclin over the coming four quarters. That being said, the product is off to a strong start, with estimated demand of approximately $17mm, based on recent weekly IMS trends. We believe the product will contribute approximately $18mm to 2005 revenues, with the product growing to approximately $56mm in 2009.

We expect that Connetics will experience a considerable slowdown in top-line growth over the coming quarters, regardless of whether or not Velac is significantly delayed. Connetics trailing 12-months revenue growth (through Q1:05) has been over 100%. If Connetics experiences a 12-18 month delay in approval of Velac, we estimate that its trailing 12-month revenue growth will decelerate to 64%, 47%, 26% and 17% between Q2:05 and Q1:06. If Velac is delayed by 3-months, we believe this would add an incremental 4-5% to Connetics' top-line growth starting in Q3:05.

Figure 2: Connetics - Trailing 12-months revenues

	Q1'05	Q2'05	Q3'05	Q4'05	Q1'06	Q2'06	Q3'06	Q4'06
Trailing 12-months Rev	$162	$168	$178	$182	$189	$195	$205	$218
% Growth	101%	65%	47%	26%	17%	16%	15%	20%
Add: Velac - 6/25/05	-	-	-	6.0	7.0	8.0	3.0	3.0
Adj.'d Trailing 12-month Rev	$163	$169	$178	$188	$196	$203	$208	$221
% Growth	101%	64%	51%	30%	21%	20%	17%	17%

It should be noted that our model currently assumes that generic versions of Soriatane enter the market in H2:06. If this does not occur, we estimate that it would contribute an additional 2-4% to top-line growth in H2:06.

VALUATION AND OUTLOOK

In our opinion, the Connetics' valuation is determined by three components: 1) the operations of the company, excluding Soriatane (due to its generic risk), 2) the cash generating abilities of Soriatane, and 3) the risk adjusted value of potential unknown events (such as the timing approvals/launches for Velac, Clin-RA and Differin-BP). We have provided figures highlighting the metrics by which we have valued each of these three components (figures 3-5). In summary, we believe that the stock is trading close to its fair value based on these three metrics.

The company's next major catalyst is its pending PDUFA date for Velac on 6/25/05 and we expect that the product approval will be delayed by approximately one quarter. In our opinion, this would be the result of either an approvable letter or an extension of the PDUFA date. In this scenario (60% probability), we expect the stock will trade flat to modestly higher, as fears of a longer delay would be eased. In the case of a long delay (12-18 months, 20% probability), requiring the generation of additional clinical data, we suspect that the stock would trade into the mid-teens. Conversely with an approval (20% probability), we would believe the stock could rebound into the low/mid-$20's.

Figure 3: Connetics –Value of EPS – Excluding Soriatane

Connetics 2007 EPS - ex. Soriatane	**$0.72**	**$0.72**
Multiple Range	25	30
Discount Rate	20.0%	20.0%
Value of CNCT - Ex Soriatane	**$15.00**	**$18.00**
Add: Soriatane Val	$2.50	$2.50
Target Price	**$17.50**	**$20.50**
Risk Adjusted Value of Potential Changes	$1.20	$1.20
Target Price	**$18.70**	**$21.70**

Figure 4: Value of Soriatane Cash Flows

Soriatane Value	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
Revenues	**$53.6**	**$69.0**	**$72.4**	**$76.0**	**$79.8**	**$83.8**
COGS	($5.4)	($6.9)	($7.2)	($7.6)	($8.0)	($8.4)
Interest Income	$0.9	$0.7	$0.8	$0.8	$0.9	$0.9
Pretax	**$49.1**	**$62.8**	**$65.9**	**$69.2**	**$72.7**	**$76.3**
Tax Expense	$1.5	$22.0	$23.1	$24.2	$25.4	$26.7
Net Impact	**$47.6**	**$40.8**	**$42.9**	**$45.0**	**$47.3**	**$49.6**
Discount Rate	-	30.0%	40.0%	50.0%	60.0%	70.0%
# Years	-	0	1	2	3	4
PV – Annual	**-**	**$40.8**	**$30.6**	**$20.0**	**$11.5**	**$5.9**
Total PV	**-**	**$40.8**	**$71.4**	**$91.4**	**$103.0**	**$108.9**
Per Share	-	**$0.97**	**$1.68**	**$2.12**	**$2.37**	**$2.48**

Figure 5: EPS & Value Impact of Potential Changes to Model

EPS Impact - Per Factor										
Factor	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**Multiple on '07 EPS**	**$ Impact**	**Probability**	**Adjusted Impact**
Taxed EPS - Ex Soriatane	($0.41)	($0.42)	$0.34	$0.72	$1.41	$2.06	-	-	-	-
Velac launch Q4:05	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	25	$0.00	60.0%	$0.00
Approval on 6/25/05	-	$0.10	$0.05	$0.07	$0.07	$0.07	25	$1.75	10.0%	$0.18
15-Month Velac Delay	-	($0.08)	($0.39)	($0.21)	($0.22)	($0.22)	25	($5.25)	30.0%	($1.58)
15-Month Clin-RA Delay	-	$0.08	$0.33	$0.42	$0.46	$0.50	25	$10.50	35.0%	$3.68
No Generic Soriatane	-	-	$0.02	$0.31	$0.55	$0.74	25	$7.75	20.0%	$1.55
Differin-BP (15% impact)	-	-	($0.07)	($0.21)	($0.28)	($0.35)	25	($5.25)	50.0%	($2.63)
Sum										**$1.20**

Figure 6: Connetics EPS Model

Revenues	**2004**	**Q1'05**	**Q2'05**	**Q3'05**	**Q4'05**	**2005**	**2006**	**2007**	**2008**	**2009**
Product	142.0	42.1	44.8	46.3	53.5	186.7	241.0	273.9	327.1	380.5
Royalty	2.3	0.2	0.3	0.4	0.5	1.3	4.9	10.0	15.5	20.2
Contract & Other	-	-	-	-	-	-	-	-	-	-
Total Revenues	**144.3**	**42.3**	**45.1**	**46.7**	**54.0**	**188.0**	**246.0**	**283.8**	**342.6**	**400.7**
% Growth	99.3%	69.8%	17.9%	25.0%	23.2%	30.3%	30.8%	15.4%	20.7%	16.9%
COGS	12.7	3.8	4.0	4.2	5.0	16.9	22.9	26.9	33.1	39.6
Licensing Amort.	11.8	3.4	3.4	3.4	3.4	13.6	10.4	11.4	12.3	13.2
R & D	21.3	5.9	6.5	6.8	6.8	26.0	30.2	34.4	38.5	42.7
SG&A	72.2	27.8	27.7	22.5	22.0	100.0	117.0	133.0	149.0	163.0
Operating Income	**26.4**	**1.4**	**3.5**	**9.8**	**16.8**	**31.5**	**65.5**	**78.1**	**109.8**	**142.1**
Interest Income	1.5	0.5	1.0	1.1	1.1	3.6	3.3	8.8	11.8	15.8
Interest Expense	(3.2)	(0.8)	(0.9)	(0.9)	(0.9)	(3.3)	(3.4)	(5.8)	(4.9)	(4.0)
Other	(3.4)	(0.1)	-	-	-	(0.1)	(63.9)	-	-	-
Pretax Income	**21.2**	**1.0**	**3.7**	**10.0**	**17.0**	**31.7**	**65.4**	**81.1**	**116.6**	**153.9**
Tax Expense	1.5	0.1	0.4	1.0	1.7	3.2	16.2	28.4	40.8	53.9
Net Income	**19.7**	**0.9**	**3.3**	**9.0**	**15.3**	**28.6**	**49.2**	**52.7**	**75.8**	**100.1**
Interest Add-Back	-	0.6	0.6	0.6	0.6	2.3	2.3	2.3	2.3	2.3
Net Income, Adjusted	**-**	**1.5**	**3.9**	**9.5**	**15.9**	**30.9**	**51.5**	**55.0**	**78.1**	**102.4**
Net Income - Fully Taxed	**13.8**	**1.3**	**3.0**	**7.0**	**11.7**	**22.9**	**44.8**	**55.0**	**78.1**	**102.4**
EPS	**$0.52**	**$0.04**	**$0.09**	**$0.23**	**$0.38**	**$0.73**	**$1.21**	**$1.28**	**$1.80**	**$2.33**
% Growth	-	-27%	-55%	135%	125%	41%	65%	6%	41%	30%
EPS - Fully Taxed	**$0.36**	**$0.03**	**$0.07**	**$0.17**	**$0.28**	**$0.54**	**$1.05**	**$1.28**	**$1.80**	**$2.33**
% Growth	-	-17.4%	-46.8%	156.5%	136.2%	51.9%	93.2%	21.6%	40.6%	29.8%
Share Count	**38.4**	**42.2**	**42.2**	**42.2**	**42.2**	**42.2**	**42.6**	**43.1**	**43.5**	**43.9**
% Growth	18.1%	17.6%	1.4%	10.9%	10.6%	9.8%	1.0%	1.0%	1.0%	1.0%

Figure 7: Connetics – Revnues Projections

	2004	Q1'05	Q2'05	Q3'05	Q4'05	2005	2006	2007	2008	2009
Product Revenues										
Olux (Non-Scalp Psoriasis)	61.8	15.8	16.7	17.6	17.8	67.9	74.6	79.9	83.8	87.2
Luxiq (Scalp Dermatoses)	23.8	5.7	6.2	6.9	7.0	25.8	28.6	30.4	31.6	32.5
Evoclin (Acne)	2.9	3.1	4.5	5.0	5.5	18.0	28.0	40.0	49.0	56.0
Soriatane - (Severe Psoriasis) - WW	53.6	17.6	17.4	16.8	17.2	69.0	63.7	46.8	33.2	23.8
Total Product Revenue	**142.0**	**42.1**	**44.8**	**46.3**	**47.5**	**180.7**	**195.0**	**196.9**	**197.6**	**199.6**
Pipeline Products										
Velac (Acne)	-	-	-	-	6.0	6.0	34.0	50.0	65.0	80.0
Desilux (Emolient)	-	-	-	-	-	-	7.0	13.0	22.0	28.0
Primolux-EF (Non-Scalp Psoriasis)	-	-	-	-	-	-	5.0	9.0	13.0	16.0
Luxiq EF (Scalp Dermatoses)	-	-	-	-	-	-	-	2.0	3.5	5.0
Extina (Antifungal)	-	-	-	-	-	-	-	3.0	10.0	20.0
Calcipotriene Foam (Mild/Mod Psoriasis)	-	-	-	-	-	-	-	-	6.0	12.0
Clinda/BP Foam (Acne)	-	-	-	-	-	-	-	-	10.0	20.0
Topical Soriatane (Mild/Mod Psoriasis)	-	-	-	-	-	-	-	-	-	-
Total Pipeline Contribution	**-**	**-**	**-**	**-**	**6.0**	**6.0**	**46.0**	**76.9**	**129.4**	**180.9**
Total Product Sales	**142.0**	**42.1**	**44.8**	**46.3**	**53.5**	**186.7**	**241.0**	**273.9**	**327.1**	**380.5**
Total Royalty	**2.2**	**0.2**	**0.3**	**0.4**	**0.5**	**1.3**	**4.9**	**10.0**	**15.5**	**20.2**
Total Revenues	**144.1**	**42.4**	**45.1**	**46.7**	**54.0**	**188.0**	**246.0**	**283.8**	**342.6**	**400.7**

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EXHIBIT 48

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Transgenic Mouse Models: Their Role in Carcinogen Identification

John B. Pritchard, John E. French, Barbara J. Davis, and Joseph K. Haseman

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Transgenic Mouse Models: Their Role in Carcinogen Identification

John B. Pritchard[1], John E. French[2], Barbara J. Davis[3], and Joseph K. Haseman[4]

Laboratory of Pharmacology and Chemistry[1] and Laboratory of Experimental Carcinogenesis and Mutagenesis[2], Environmental Toxicology Program

Laboratory of Women's Health[3], and the Biostatistics Branch[4], Environmental Biology and Medicine Program

Division of Intramural Research
National Institute of Environmental Health Sciences
Research Triangle Park, NC 27709

Address Correspondence to:

Dr. John B. Pritchard
Laboratory of Pharmacology and Chemistry
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, NC, 27709

Phone: (919) 541-4054
Fax: (919) 541-5737
pritchard@niehs.nih.gov

Running Head: Transgenic Models

Abbreviations (Text):

NTP	=	National Toxicology Program
MAPKK	=	mitogen-activated protein kinase kinase
Trp53+/-	=	Trp53 heterozygous null allele (+/-) mouse
Tg.AC	=	Tg.AC (*v-Ha-ras)* mouse
*ras*H2	=	hemizygous for the human *c-Ha-ras* transgene
ILSI	=	International Life Sciences Institute
ROC	=	Report on Carcinogens
IARC	=	International Agency for Research on Cancer

Abbreviations (Tables):

+	=	positive
-	=	negative
±	=	equivocal
f	=	feed
g	=	gavage
d	=	dermal
ip	=	intraperitoneal injection
i	=	inhalation
sc	=	subcutaneous
wb	=	whole body routes of exposure
nt	=	not tested or no published record
sal	=	*salmonella* mutagenicity assay
mn	=	*in vivo* micronuclei genotoxicity assay

Keywords:

carcinogen
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mouse
model
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transgenic

Abstract:

This report examines existing data on the use of transgenic mouse models for identification of human carcinogens. It focuses on the three most extensively studied of these mice – Trp53+/-, Tg.AC, and RasH2 – and compares their performance with the traditional 2-year rodent bioassay. Data on a total of 99 chemicals were evaluated. Using the IARC/ROC calls for the carcinogenicity of these chemicals to humans as the standard for comparison, a variety of potential testing strategies were evaluated ranging from individual transgenic models to combinations of these 3 models with each other and with traditional rodent assays. The individual transgenic models made the "correct" calls (positive for carcinogens; negative for noncarcinogens) for 77-81% of the chemicals, with an increase to as much as 88 % using combined strategies (e.g., Trp53+/- for genotoxic chemicals and RasH2 for all chemicals). For comparison, identical analysis of chemicals in this data set that were tested in the 2-year, 2-species rodent bioassay yielded "correct" calls for 69 % of the chemicals. Although the transgenic models had a high percentage of correct calls, they did miss a number of known or probable human carcinogens; whereas, the bioassay missed none of these chemicals. Therefore, "mixed" strategies using transgenic models and the rat bioassay were also evaluated. These strategies yielded ~85 % correct calls, missed no carcinogens, and cut the number of positive calls for human non-carcinogens in half. Overall, the transgenic models performed well, but important issues of validation and standardization need further attention to permit their regulatory acceptance and use in human risk assessment.

Introduction:

The National Toxicology Program (NTP) is charged with the responsibility for evaluating the toxicity and carcinogenicity of environmental agents, developing and validating improved testing methods, and strengthening the science base in toxicology. A variety of endpoints are used to assess the systemic toxicity of environmental chemicals, but the mainstay of the chemical carcinogenesis effort has been the 2-year rodent bioassay. This highly standardized method has been widely adopted throughout the world. However, like any other approach it has its strengths and weaknesses. In particular, the 2-year assay is expensive, both in resources and time required and in the numbers of animals needed. Thus, the advent of transgenic and gene knockout technology in the early 1980's and increasing knowledge of the mechanisms involved in carcinogenesis, led a number of investigators to examine whether faster, less costly, and more predictive models might be developed. NIEHS has been actively involved in this effort for more than a decade and several model systems utilizing transgenic and knockout models have been investigated (Bucher 1998;Eastin, et al. 1998;Tennant 1993;Tennant, et al. 1995).

Transgenic models have a number of potential advantages for use in carcinogen identification programs. For example, because tumors arise more quickly in the genetically engineered models, the assays can be more rapid. For the studies reviewed here, the assay length was 24-26 weeks, significantly shorter than the standard 2-year rodent bioassay. Transgenic models may also provide the opportunity to reduce animal numbers used in testing. Shorter assays using fewer animals could also reduce the overall cost of testing programs. However, proprietary issues and the limited availability of some models may impact cost savings. Furthermore, with appropriate model selection, it may become possible to more accurately predict the human response, contributing directly to the ease and effectiveness of risk assessment and regulatory decisions.

Finally, by virtue of the specific genetic modification(s) in transgenic models, it should be possible to gain additional insights into the mechanisms involved in tumor induction and development. Such insights would facilitate identification of important mechanisms participating in the tumor response and chemical features associated with carcinogenesis.

Although they have great promise, transgenic models also have actual or potential limitations for use in a carcinogen identification effort. For example, many current transgenic models (including those evaluated here) have mutations in only one pathway that may, or may not, be relevant to human cancer processes for a given chemical. In addition, the specific gene defect may influence tumor development and type, increasing the difficulty of modeling the human response. Likewise, the strain (genetic) background can influence tumor type, incidence, and location. Thus, short-term, gene-specific transgenic assays may lose biological information obtained in longer-term bioassays, *e.g.,* multiple target organ effects and/or interactions of time and age that are important in chemical carcinogenicity. These issues do not preclude the use of transgenic models, but they must certainly be considered in their development and selection, and in interpretation of data obtained using transgenic models.

Given the potential and the limitations of the transgenic models, the goals of the current assessment are to (1) review progress in this field of research, (2) determine if the models reviewed show sufficient merit for use in a carcinogen identification program, and (3) identify research needs and knowledge gaps that should be addressed to increase the effectiveness of transgenic models.

Review of Research Progress:

Many transgenic models are available for various investigational uses. However, three transgenic models have been most widely used for carcinogen identification: Trp53+/-, Tg.AC, and RasH2. These three models were selected for this assessment because they have the extensive data set needed for this analysis. Their selection does not indicate that they are deemed superior *a priori* to other transgenic models.

Extensive recent reviews of these three models have been published (17-24) and only their main features are briefly reviewed here. They were developed based on dysregulation of either the Trp53 tumor suppressor gene or the *ras*-protooncogene, both of which are critical to cancer development and represent the two main classes of human cancer genes. The p53 protein suppresses cancer in humans and rodents and is mutated or dysfunctional in more than 50 % of all cancers (Donehower, et al. 1992;Hollstein, et al. 1991;Weinberg 1991a). As a transcription factor, p53 regulates the activity of a variety of genes involved in cell cycle arrest, apoptosis, anti-angiogenesis, differentiation, DNA repair, and genomic stability (el-Deiry 1998;Prives and Hall 1999). The *ras* protooncogene protein (H-, K, and N-*ras* isoforms) is integral to cell proliferation through signaling by growth factors and noxious agents (chemicals, UV radiation, etc.) that act via the mitogen-activated protein kinase kinase (MAPKK) pathway (Campbell, et al. 1998;Gupta, et al. 2000;Pruitt and Der 2001). Activation and dysregulation of *ras* through mutations at specific sites within the gene are often observed in both human and rodent cancers (Bos 1989;Hruban, et al. 1993;Vogelstein, et al. 1990;Yunis, et al. 1989). In addition, increased expression of oncogenic *ras* protein is often seen during tumorigenesis by aneuploidy of the *ras* bearing chromosomes, which may be analogous to over-expression of induced transgenic *ras* protein. Overall, *ras* is over-expressed in well over 50 % of all cancers.

The *Trp*53 heterozygous null allele (+/-) mouse: This model uses B6129 N5 mice heterozygous for a wild type Trp53 tumor suppressor gene and a null allele that is not transcribed or translated (Donehower, et al. 1992;Harvey, et al. 1993). These Trp53 heterozygotes (+/-) have a low spontaneous tumor incidence up to 9 months of age, but have increased spontaneous tumor rates thereafter with approximately 50 % survival at 18 months. Exposure to positive control and test agents between 7 and 33 weeks of age is relatively free of the development of spontaneous tumors, thus allowing a clear distinction between induced and sporadically occuring tumors that may confound long term chronic cancer bioassays (Haseman and Elwell 1996;Karstadt and Haseman 1997). It appears to be particularly useful as an *in vivo* test for mutagenic carcinogens (Donehower, et al. 1992;Eastin, et al. 1998;Harvey, et al. 1993;Kemp, et al. 1993;Kemp, et al. 1994;Tennant, et al. 1995). In human cancers, where mutations have been found in up to 50 % of all tumors (Greenblatt, et al. 1994;Hollstein, et al. 1991), point mutations or deletions in one allele of the Trp53 gene that create a heterozygous allelic state are usually accompanied by loss of the normal allele (loss of heterozygosity or LOH) (Weinberg 1991b). Since Trp53 +/- mice only carry one copy (germ line) of the gene, these mice were expected, according to the Knudson *et al.* two-hit hypothesis (Knudson 1996;Knudson, et al. 1975), to show a shorter latency period for tumors induced by genotoxic agents. However, there is evidence that the acceleration of tumorigenesis in Trp53 +/- mice may be due to a gene dosage effect and a haploinsufficient phenotype such that a second (p53 LOH) event is not required (French, et al. 2001;Venkatachalam, et al. 1998).

The Tg.AC (*v-Ha-ras*) mouse: The Tg.AC transgenic mouse model provides a reporter phenotype (skin papillomas) in response to either genotoxic or non-genotoxic carcinogens, including tumor promoters (Spalding, et al. 1999;Spalding, et al. 1993;Tennant, et al. 1999).

Tg.AC mice are hemizygous for a mutant *v-Ha-ras* transgene. The model was developed by Leder et al. (Leder, et al. 1990), with an inducible -globin promoter driving the expression of a mutated *v-Ha-ras* oncogene and is regarded as a genetically initiated model. With the exception of the bone marrow, constitutive expression of the transgene cannot be detected in adult tissues. The transgene is transcriptionally silent until activated by full-thickness wounding, UV irradiation, or specific chemical exposure (Cannon, et al. 1997;Trempus, et al. 1998). Topical application of carcinogens to the shaved dorsal surface of Tg.AC mice induces epidermal squamous cell papillomas or carcinomas, a reporter phenotype that defines the activity of the chemical. The oral route of administration can also generate tumor responses in the skin of Tg.AC mice and in addition lead to squamous cell papillomas and/or carcinomas of the forestomach. To date, the appearance of either spontaneous or induced tumors has been shown to require activation of transgene expression. However, the mechanism of response by the Tg.AC model to chemical carcinogens is not yet understood.

The *ras*H2 mouse: The rasH2 mouse is hemizygous for the human *c-Ha-ras* transgene under control of its endogenous promoter and enhancer sequences. It was developed by Saitoh *et al.* (Saitoh, et al. 1990) in CB6F1 mice to evaluate the association of chemically induced transgene expression and tumor induction (Katsuki, et al. 1991;Yamamoto, et al. 1996;Yamamoto, et al. 1998a). The transgene encodes a prototype c-H-ras gene product, p21 that does not induce transformation in NIH3T3 cells. Approximately 3 copies of the human transgene were integrated into the mouse genome in a tandem array through pronuclear injection (Suemizu, et al. 2002). Expression of the transgenic protein is observed in normal tissues and increased approximately 2-fold in chemically induced tumors (Maruyama, et al. 2001). Mutation of the endogenous mouse ras genes or of the transgene is infrequent and unpredictable (Katsuki, et al.

1991); suggesting that a 2-3-fold increase in *ras* protein expression is sufficient to cooperate with other carcinogen-induced changes (genetic and/or epigenetic) to predispose this mouse to development of neoplasia.

Merits of the Models:

Data Collection – To assess the potential merit of the three transgenic models in a research and testing program, we assembled available information on responses to chemical treatment in each model (Tables 1-3). The primary sources of these data were the recent publications of the International Life Sciences Institute (ILSI) Assay Working Groups for the Trp53+/-, Tg.AC, and RasH2 Mouse Alternative Models (Popp 2001;Robinson and MacDonald 2001), NTP evaluations, and published independent laboratory research using alternative or conventional rodent models for carcinogen identification (For specific references see Tables 1-3). The resulting data set consists of 99 chemicals that were tested at the maximum tolerated dose (MTD) or proportional fractions of MTD as determined by toxicokinetic and range finding studies in the test strain using positive and negative controls groups and non-genetically altered coisogenic reference controls. In reviewing this literature, it was apparent that dosing routes, study duration, number of animals per group, and extent of histopathologic evaluation varied between studies and chemicals. Despite these limitations, for the purposes of this analysis, peer-reviewed published findings were accepted as reported.

Criteria for Analysis – Because the goal of the NTP carcinogenicity testing is prediction of human carcinogenicity of chemicals, the merit of the transgenic models was evaluated by determining their ability to identify human carcinogens. Classification of human carcinogens was based on evaluations by the NTP Report on Carcinogens (ROC) and the International Agency for

Research on Cancer (IARC) chemical evaluations/classifications. Both the NTP and IARC assessments are based on comprehensive evaluations of all relevant human and animal data from the published literature. The designation of an agent as a "known human carcinogen" by the IARC (Group 1) or the NTP ROC requires definitive data from human epidemiological studies, or strong mechanistic data from human systems in conjunction with similar mechanistic and cancer data from experimental animals. Less convincing evidence (*e.g.,* limited human data and/or sufficient animal data) will generally lead to the designation of the agent as a "probable (Group 2A) or "possible" (Group 2B) human carcinogen by IARC or a "reasonably anticipated" human carcinogen NTP ROC. A chemical that shows inadequate evidence of carcinogenicity in humans and animals will generally result in an IARC designation of "not classifiable" (Group 3). The NTP ROC has no equivalent and does not list such chemicals. Rodent carcinogenicity was not used as the primary targeted response in our analysis. Nevertheless, for completeness we did consider the correlation of each transgenic model with the outcomes of NCI/NTP long-term rodent tests. We also examined whether these transgenic assays were more, or less, accurate in predicting human carcinogenicity of genotoxic versus non-genotoxic chemicals, as defined by either a positive result in the Salmonella (Ames) test and/or in vivo rodent micronucleus assay.

A total of ninety-nine chemicals have been studied in one or more of these three transgenic models. For this analysis, these chemicals were divided into three groupings: **(i)** Known human carcinogens (IARC Group 1 and/or NTP ROC "known" – 14 chemicals, Table 1); **(ii)** Probable/ Possible human carcinogens (IARC Groups 2A and 2B or NTP ROC "reasonably anticipated" –32 chemicals, Table 2); and **(iii)** Chemicals with inadequate evidence of carcinogenicity (IARC Group 3, NTP bioassay negative, and/or not listed by ROC or IARC – 53 chemicals, Table 3).

Tables 1-3 identify each chemical by CAS number and give the IARC and/or the NTP ROC evaluations. For those chemicals evaluated in the NTP rodent bioassay, carcinogenicity results are given for each sex-species group (male rats, female rats, male mice, female mice). Genotoxicity outcomes from the Salmonella (Ames) assay and the *in vivo* micronuclei assays are also given. Finally, the results of carcinogenicity testing in each of the three transgenic models are given. The route of administration is noted, as well as the published reference source. For chemicals tested more than once in the transgenic models, each result is given separately.

For each of the transgenic models and for the rodent bioassay, a chemical is designated as a carcinogen if positive (carcinogenic) effects were found in one or more of the sex-species groups. Similarly, a chemical found to be positive in either the Salmonella assay or the *in vivo* micronuclei assay is considered to be genotoxic.

Analysis of the Models -- Based on the 99 chemical database from Tables 1-3, ten possible strategies were considered for using transgenic models to identify chemicals as known or suspected human carcinogens or as noncarcinogens. For comparison, the standard two-year, two-species rodent bioassay and a modified strategy using the rat bioassay in conjunction with genotoxicity were also analyzed in an identical fashion. Thus, twelve strategies in all were considered. They are:

Strategy 1: Trp53+/- model

Strategy 2: Trp53+/- model, but only for genotoxic chemicals

Strategy 3: Tg.AC model

Strategy 4: RasH2 model

Strategy 5: Trp53+/- model for genotoxic chemicals; RasH2 model for nongenotoxic chemicals

Strategy 6: Trp53+/- model for genotoxic chemicals; RasH2 model for all chemicals

Strategy 7: Trp53+/- model for genotoxic chemicals; Tg.AC model for nongenotoxic chemicals

Strategy 8: Trp53+/- model for genotoxic chemicals; Tg.AC model for all chemicals

Strategy 9: NTP Bioassay

Strategy10: NTP Rat Bioassay plus the Tg.AC model for nongenotoxic chemicals or the Trp53+/- model for genotoxic chemicals

Strategy 11: NTP Rat Bioassay plus the RasH2 model for nongenotoxic chemicals or the Trp53+/- model for genotoxic chemicals

Strategy 12: NTP Rat Bioassay plus genotoxicity

When evaluating strategies that were conditional on genotoxicity (Strategies 5-8, 10-11), the following conventions were established: (i) a chemical was considered genotoxic if either the Salmonella or in vivo micronuclei assays were positive; (ii) a chemical was considered non-genotoxic only if both assays were negative; and (iii) when a chemical's genotoxicity could not be determined definitively (*i.e.,* negative in one assay and not tested in the other), the chemical was excluded from the analysis, unless the genotoxicity status of the chemical had no impact on the transgenic mouse result (*i.e.,* both transgenic models were positive or both were negative).

A valid transgenic rodent model should successfully identify (test positive) the IARC/NTP known or suspected human carcinogens listed in Tables 1 and 2. Likewise, such a model should identify as noncarcinogens (test negative) those chemicals in Table 3 that were shown in NTP long-term bioassays to be negative. While many of the remaining chemicals in Table 3 were positive in a long term rodent bioassay, these results were not considered by the IARC and/or NTP ROC to be sufficiently convincing to merit the categorization of the chemical as a known, possible, probable, or reasonably-anticipated human carcinogen. For these chemicals, it is

uncertain if the response of the transgenic models should be positive or negative as carcinogens. Thus, our initial analysis (Table 4) included only those Group 3 chemicals with negative results in the NTP rodent bioassay. Table 5 examines the same data set as Table 4, but considers each IARC/ROC classification separately to insure that pooling carcinogen groups in these analyses did not lose important distinctions between assay responses to strong or weak carcinogens.

In addition, as summarized in Table 6, we have conducted a second analysis in which all chemicals in Table 3 are regarded as human noncarcinogens, *i.e.,* we have assumed, for the sake of direct comparison between transgenic and traditional NTP bioassays, that more extensive testing of these chemicals would confirm their lack of human carcinogenicity. This assumption permits exactly the same criteria to be applied to all strategies, transgenic and traditional alike. Finally, although human carcinogenicity was used as the targeted response in our analysis, a similar analysis was conducted in which the transgenic assay responses were compared with the results of the NTP bioassay (Table 7).

Results and Discussion:

Scope of analysis — Before discussing the analysis itself, it is critical to reiterate the precise limitations and assumptions implicit in our analysis. First, this evaluation was limited to those chemicals with definitive published transgenic results available at the time of our analysis. We recognize that this is a dynamic field of research. Thus, additional transgenic studies will become available over time, and it is possible that some chemicals listed in Tables 1-3 could be reclassified after consideration of such new data. However, we suggest that the analyses for these 99 chemicals are sufficiently robust that the addition, subtraction, and/or re-assignment of chemicals will not alter the conclusions, provided that uniform criteria are applied.

Second, optimal protocol designs for specific transgenic animal cancer bioassays have not been identified and validated. Thus, the study designs that form the basis of this evaluation may differ from each other with regard to study duration, sample sizes, dose selection strategy, number of doses, tissues examined, methods of statistical analysis, historical controls, and the use of positive and negative controls.

Third, we made no interpretative decisions ourselves in regard to study results. For assessments of possible human cancer risk, we relied upon the authoritative judgments of the IARC and the NTP Report on Carcinogens. Likewise, we accepted the study authors' interpretations of the data. However, there was uniformity of study design and interpretation for a sizable number of the studies involved in the ILSI Alternatives to Carcinogenicity consortium. It was beyond the scope of this research analysis to reevaluate and reinterpret each individual study.

Fourth, we recognize and acknowledge that a "positive" transgenic study may reflect a wide range of carcinogenic responses, with some positive results being limited to a marginal increase in a single tumor type in a single sex-species group, while others reflect striking multi-site, multi-sex, carcinogenic effects. While future refinements in statistical evaluation may permit sub-classification and rank order documentation for the various "positive" transgenic responses, we have not attempted to do so at this stage in the development of transgenic rodent bioassays.

Finally, we recognize that certain chemicals listed in Table 3 may ultimately be shown to be "known" or "suspected" human carcinogens, especially those with positive rodent bioassay results. However, our current state of knowledge does not permit a higher classification of these chemicals. As noted below, the frequency of positive transgenic results for Table 3 chemicals was essentially the same for those chemicals that were evaluated by the IARC (and assigned to Category 3) and those that were not yet evaluated and are thus unclassified. This suggests that there are few, if any, important human carcinogens among the "unclassified" chemicals in Table 3.

Performance of strategies _ The overall performance of each transgenic strategy is summarized in Table 4. With the caveat that data on all chemicals were not available for each model and thus, that the subset of chemicals actually tested in each model may influence the specific outcomes reported, each of the three transgenic mouse models predicted human carcinogenesis for 77-81 % of the chemicals studied in that model, ranging from 77 % for the Trp53+/-, 78 % for the Tg.AC, and 81 % for the RasH2. Use of the Trp53+/- for only genotoxic chemicals increased its predictiveness to 84 %. The combined strategies that use more than one transgenic model (Strategies 5-8; as defined above) were somewhat more predictive, ranging from 78-88 %.

The best strategy (Trp53+/- for genotoxic chemicals and RasH2 for all chemicals; Strategy 6) correctly predicted the human outcome for 88 % of the agents (Table 4). Strategy 8 (Trp53+/- for genotoxic chemicals and Tg.AC for all chemicals) was only slightly less predictive (85 %).

Our initial analysis (Table 4) defined the targeted population of "human carcinogens" as the pool of chemicals from Tables 1 and 2, in which IARC classifications ranged from 1 to 2B. A further breakdown of these chemicals is given in Table 5. Note that **(i)** the transgenic models (considered collectively) are more apt to be positive for the more certain human carcinogens (IARC Categories 1 and 2A) than for the less certain human carcinogens (Category 2B); **(ii)** there is a striking difference in the proportion of positive transgenic responses between the 1/2A/2B chemicals and the Category 3 chemicals or those not evaluated; and **(iii)** the IARC Category 3 chemicals and those not evaluated show a similar rate of overall transgenic responses – indicating that most of the unclassified chemicals listed in Table 3 may be human noncarcinogens.

Our initial analysis (Table 4) was somewhat restrictive, in that it defined human noncarcinogens as being only those chemicals from Table 3 with negative NCI/NTP rodent bioassay results. However, Table 5 suggests that it is reasonable to expand this classification and regard all Table 3 chemicals as human noncarcinogens. This analysis is summarized in Table 6, which allows more direct comparison of the performance of the transgenic models with the traditional NTP two-species bioassay, transgenic and traditional testing strategies each show strengths and weakness. Importantly, these strengths and weaknesses differ. For the transgenic models, particularly the RasH2 and the Trp53+/-, there are relatively few positive findings for noncarcinogens (*i.e.,* Group 3 chemicals, either known negatives or chemicals unlisted by

IARC/ROC, that gave evidence of carcinogenicity in the assay). In fact, as shown in Table 4, RasH2 and Trp53+/- have no positive results for noncarcinogens if those Group 3 chemicals that lack a negative rat and mouse bioassay are eliminated from the analysis (in effect, eliminating those chemicals with greater uncertainty as to their carcinogenic potential). The Tg.AC model was more prone to this type of error than the other two transgenic models reviewed (Tables 4 and 6). The combined transgenic strategies (Strategies 5-8) did not improve predictability.

A more frequent shortcoming of the transgenic models (including, those strategies using multiple transgenic models) was the number of negative tests for known or suspected human carcinogens, *i.e.,* those listed in Tables 1 and 2 (Tables 4 and 6). For example, even the most predictive combination (the combined results of Trp53+/- for genotoxic chemicals plus Tg.AC for nongenotoxic chemicals; Strategy 7) still had 6 negative results for IARC/NTP known carcinogens among the total of 49 chemicals tested in both (Table 6).

In contrast, the NTP two-species bioassay identified all IARC/NTP known/probable human carcinogens (Tables 1 and 2). Thus, as shown in Table 6 (Strategy 9), among the 58 chemicals evaluated in the NTP bioassay, there were no negative results for known human carcinogens. However, this is not without a downside in the form of numerous positive findings for chemicals that are considered to be noncarcinogens in humans (Table 3). In this data set, there were 18 positive assay results for IARC/ROC noncarcinogens among a total of 58 chemicals tested, or 31 % (Table 6). Certainly, there is a cost of this type of error as well, specifically unneeded regulation and/or additional testing. It is this propensity for positive findings for chemicals considered to be human noncarcinogens that yielded the surprisingly low 69 % concordance between the standard NTP bioassay and human cancer – surprising because many of the ROC

and IARC calls are based in large part on animal data and the NTP bioassay in particular. In fact, all three transgenic models had a modestly higher concordance with human carcinogens (Tables 1 and 2) than the rodent 2-year bioassay (Trp53+/- 81 %, RasH2 75 %, and Tg.AC 74 %; Table 6). Of course, this difference is also reflected in the modest success (54-78 %) of the transgenic models as predictors of the bioassay response (Table 7).

It should be emphasized that it is possible that many of the 18 NTP rodent carcinogens labeled in our analysis as "Positive for Noncarcinogens" (Table 6, Strategy 9) may ultimately prove to be actual human carcinogens, as additional data becomes available. However, at this time the positive rodent data are not sufficiently compelling for the IARC or the NTP ROC to consider these chemicals to be known, probable, possible, or reasonably anticipated human carcinogens. In those rare cases where the IARC and ROC disagreed (*e.g.,* DEHP) we used the most recent call. Moreover, these 18 chemicals collectively were positive in only 27 % (8/30) of the three transgenic assays evaluated, as compared with 66 % (29/44) positive transgenic assays conducted on the 24 known/probable carcinogens. This difference strongly suggests that the transgenic assays are selectively identifying the trans-species carcinogens.

Since both transgenic models and the bioassay have strengths and weakness in correctly identifying carcinogenic chemicals, we examined the performance of composite strategies using both transgenic and conventional rodent models to determine if such a strategy might capitalize on the strengths of both types of models. Strategies 10 and 11 address this possibility (Table 6). Strategy 10 (rat bioassay for all chemicals plus the Trp53+/- model for genotoxic agents or the Tg.AC for non-genotoxic chemicals) provided an improvement in performance. Overall concordance increased to 84 % versus the 69 % of the bioassay itself. More importantly,

negative results for known carcinogens were completely eliminated and positive findings for noncarcinogens were reduced to 16 % (9/57) versus the 31 % (18/58) for the bioassay. A similar strategy (Strategy 11) substituting RasH2 for Tg.AC gave very similar results, with an overall concordance of 85 % (44/52), or just 15 % (8/52) with positive results for noncarcinogens.

For those chemicals evaluated in both the NTP bioassay and the transgenic models, the substitution of the transgenic models (Strategy 10: Trp53+/- for genotoxic chemicals; the Tg.AC for non-genotoxic chemicals) for the B6C3F1 mouse used in the standard bioassay resulted in a net reduction of four positive findings. Four chemicals (coconut oil diethanolamine, diethanolamine, N-methyloacrylamide and methylphenidate) were negative in the transgenic models and the NTP rat bioassay. In the B6C3F1 mouse, the first two of these chemicals produced liver tumors (both sexes) and kidney adenoma (males only). N-methyloacrylamide produced tumors of the Harderian gland, liver, lung, and ovary. Methylphenidate produced liver tumors only. None of these chemicals has been classified as a known/probable human carcinogen by the IARC or the NTP ROC (Tables 1-3).

Historically, genotoxicity has proven to be an important clue as to the likely carcinogenesis of chemicals (Ashby and Tennant 1991;Shelby 1988). In addition, as shown in Table 4, it increases the predictiveness of Trp53+/- model. Thus, to provide a more complete assessment of possible testing strategies, we compared an additional strategy (#12, Table 6) that consists of substitution of genotoxicity data for the transgenic models to be used in concert with the rat bioassay (Strategies 10 and 11, Table 6). Strategy 12 does, like the bioassay itself, avoid negative results for known carcinogens. It also has modest concordance with human carcinogenesis 67 % (44 of

66), but it has 22 positive results for noncarcinogens out of 66 chemicals (33 %). A number of the other strategies do better.

Conclusions _ Given the complementary strengths demonstrated by the transgenic models and the 2-year rodent bioassay as presented above and summarized in Table 6, it appears that a strategy employing both types of models would have advantages over either alone. Thus, Strategies 10 and 11 that employ the standard rat bioassay in conjunction with Trp53+/- for genotoxic chemicals and Tg.AC or RasH2 for non-genotoxic chemicals are promising, based on their performance with these 99 chemicals.

Research Needs:

This analysis demonstrates that transgenic models have the potential to play an important role in identification of potential human carcinogens. However, several research needs and data gaps remain to be addressed to insure that the use of transgenic models has been adequately evaluated and that protocols have been optimized or standardized for such use, critical requirements for the regulatory acceptance of transgenic model data and it's use in human risk assessment.

Validation of study design _ The study design for each transgenic model must be rigorously evaluated and optimized for the testing paradigm employed (*e.g.,* toxicity, mutagenicity, or carcinogenicity). Therefore, additional research will be required for each model evaluated and used in the NTP testing program. As mentioned previously, the testing strategies, animal numbers, duration of dosing, extent of pathology and interpretation of results varied among the studies evaluated. In particular, an optimal design for transgenic models has not yet been identified that clearly eliminates the potential for false negatives in carcinogen identification. Two possible strategies for increasing the power of the study (thereby reducing the negative results for known human carcinogens) are to increase the sample size beyond the 15 animals per group commonly used and/or to increase the duration of the study to allow more time for tumors to develop. The performance of the transgenics under these different conditions should be thoroughly investigated and standardized. A perhaps less obvious possibility would be to compile a rigorous historical control database for the various transgenic models and to make use of this information in "weight-of evidence" decisions. Many of the tissues in the transgenic mouse models have a low spontaneous tumor incidence. Thus, the occurrence of two or three of these tumors in a dosed group in a given study, although perhaps not statistically significant when tested against the concurrent controls, may nevertheless be significant when the low

historical control incidence is taken into account. For example, three of the seven negative results for known/suspected carcinogens associated with the RasH2 model (cyclosporin A, melphalan, and 1,4-dioxane) produced tumor effects that were considered equivocal. Had it been possible to consider these tumor responses in the context of a large historical control database, certain of these borderline cases might have been regarded as biologically significant, thereby reducing the number of incorrect findings.

Improve understanding of chemical outcomes _ One problem in our analysis was in identifying a rational basis to explain discordant results. For example, the most significant shortcoming of a combined (transgenic plus rat bioassay) strategy was not the negative results for known carcinogens, but rather the apparent number of positive chemicals in the rat bioassay that are not listed as known or reasonably anticipated to be human carcinogens (*e.g.,* the 10 of the 59 chemicals for Strategy 11; Table 6). How might this be improved? First, it might be possible to design additional studies to investigate whether or not these are truly noncarcinogenic chemicals. As discussed above, the targeted response in our investigation is imperfect, as it represents a scientific judgment by IARC and/or the NTP ROC regarding potential carcinogenicity based on available data. In many cases, the existing data are insufficient for a definitive decision to be made. Additional research could reduce the number of positive results for supposed noncarcinogens simply by revealing that certain of these chemicals are in fact carcinogens. Other options that might be considered to reduce this type of error include a rat transgenic model (if done in a manner that did not yield negative results for known carcinogens) or improvements in the design of the rat bioassay itself.

Development of chemical database to validate transgenics _ The data set summarized in Tables 1-3 may provide an important resource if appropriate statistical considerations could be developed to allow selection of an informative subset of chemicals for evaluation of new models and/or modification of current protocols. Such a set of chemicals that represents a spectrum of mechanisms or modes of action consistent with human carcinogenesis would not only be valuable in the context of the models discussed above, but would lend themselves to the evaluation and validation of any new model, transgenic or otherwise.

Development of Models The current analysis examined the Trp53+/-, Tg.AC, and RasH2 transgenic models because these models had the most complete data sets available. Other models are also under evaluation at the NIEHS/NTP (p16*Ink4a* and p19*Arf* deficient mice) or elsewhere (*XPA-Trp*53 deficient mice). A new generation of transgenic models is also currently being developed (Berns 2001), such as one incorporating a point mutation in k-*Ras* (Johnson, et al. 2001), or models subject to premature aging or having telomere dysfunction (Artandi and DePinho 2000;Rudolph, et al. 2001). If the NTP incorporates transgenic models into routine testing, it must necessarily include a strong research program aimed at developing the transgenic models appropriate for chemical carcinogenesis investigation and identification of carcinogens of the greatest presumptive risk to humans. As our analysis shows, the best strategy for testing may be combining different transgenic models depending on their particular attributes and utility. Thus, the NTP should actively develop such an arsenal of models. Likewise, site specific or mechanism-specific models could be developed and used with great impact in both basic research and carcinogen identification. The NTP could also develop or support research to evaluate transgenic rats or in assessment of possible refinements in the 2-year rat bioassay.

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Table 1. Comparison of results from 14 known human carcinogens[1] tested in rodent NCI/NTP cancer bioassays, Salmonella (Sal) and/or in vivo micronuclei (Mn) genotoxicity assays and/or 3 transgenic mouse cancer bioassays. Individual results were found in the cited references in parenthesis or at the IARC(IARC 2002) or the US NTP database(NTP 2002). NCI/NTP peer-reviewed conclusions are reported for male rat, female rat, male mouse; or female mouse, respectively. Results from transgenic models are presented as the summary conclusion for each route of exposure using one or both sexes of the strain used.

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
Benzene	71-43-2	1	Known	+;+;+;+ g(NTP 1986d)	-;+	+ g; + g (French, et al. 2001;Storer, et al. 2001)	+ d; + g (Blanchard, et al. 1998;Spalding, et al. 1999)	+ g (Yamamoto, et al. 1998b)
Cyclophosphamide	6055-19-2	1	Known	+;+;+;+ip (Weisburger 1977)	+;+	+ g (Storer, et al. 2001)	±d; +g (Eastin, et al. 2001)	± g;+ g; + g (Usui, et al. 2001;Yamamoto, et al. 1998b)
Melphalan	148-82-3	1	Known	+;+;+;+ ip (Weisburger 1977)	+;+	+ ip;+ ip (Eastin, et al. 1998;Storer, et al. 2001)	±d; +g (Eastin, et al. 1998;Eastin, et al. 2001)	± ip(Yamamoto, et al. 1998b)
Cyclosporin A	79217-60-0	1	Known	nt	-;-	- g;+ f;+f (Eastin, et al. 1998;Storer, et al. 2001)	+d; ± f (Eastin, et al. 1998;Eastin, et al. 2001)	± g (Maronpot, et al. 2000;Usui, et al. 2001;Yamamoto, et al. 1998a)
Diethylstilbestrol	56-53-1	1	Known	nt	-;nt	- sc ;+ f (Eastin, et al. 1998;Storer, et al. 2001)	+d; -g (Eastin, et al. 1998;Eastin, et al. 2001)	+ f (Usui, et al. 2001)
Estradiol, 17-	50-28-2	1	Reasonable	nt	-;-	± g; - g (Storer, et al. 2001)	+d; -g[2] (Eastin, et al. 2001)	- g (Usui, et al. 2001)
TCDD[3]	1746-01-6	1	Known	+;+;+;+ f (NCI/NTP 1982b)	-;nt	- g (Eastin, et al. 1998)	+ d (Eastin, et al. 1998)	nt
UVR (312-450 nM)	NA	1	Known	nt	+;+	+ d (Jiang, et al. 1999)	+ d (Trempus, et al. 1998)	nt
Asbestos fibers	1332-21-4	1	Known	-;-;nt;nt d (NTP 1988a)	nt;-	+ ip (Marsella, et al. 1997)	nt	nt

[1] As identified by the International Agency for Research on Cancer (IARC) and/or the NTP 9th Report on Carcinogens, revised January 2001.

2 Both dermal and gavage studies in the Tg.AC mice employed ethinyl estradiol (CAS No. 57-63-6), a synthetic form of estradiol, 17 .

3 2,3,7,8-Tetrachlorodibenzo-para-dioxin

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
Beryllium	7440-41-7	1	Known	nt	-;-	+ i (Finch, et al. 1998)	nt	nt
Plutonium^{239}	NA	1	Known	nt	+;+	+ i (Finch, et al. 1998)	nt	nt
Cobalt^{60}(LET)	NA	1	Known	nt	-;+	+ wb (Kemp, et al. 1994)	nt	nt
Sodium arsenate	7784-46-5	1	Known	nt	nt;nt	nt	-d (Germolic, et al. 1997)	nt
Thiotepa	52-24-4	1	Known	+;+;+;+ g (NCI/NTP 1978f)	+;nt	nt	nt	+ ip (Yamamoto, et al. 1998b)

Table 2. Comparison of results from 32 suspected human carcinogens[1] tested in rodent NCI/NTP cancer bioassays, Salmonella and/or in vivo micronuclei genotoxicity assays and/or 3 transgenic mouse bioassays. Individual results are found in the cited references in parenthesis or in the IARC(IARC 2002) or in the US NTP database(NTP 2002). NCI/NTP Peer-reviewed conclusions are reported for male F344 rat, female F344 rat, male B6C3F1 mouse; or female B6C3F1 mouse, respectively. Results from transgenic models are presented as the summary conclusion for each route of exposure using one or both sexes.

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
p-Cresidine	120-71-8	2B	Reasonable	+;+:+;+ f (NTP 1979)	+;-	+ f; + g (Storer, et al. 2001;Tennant, et al. 1995)	+ d (Tennant, et al. 1999)	+ f (Yamamoto, et al. 1998b)
Glycidol	556-52-5	2A	Reasonable	+;+;+;+ g (NTP 1990c)	+;+	- g (Tennant, et al. 1999)	- d; - g (Tennant, et al. 1999)	+ g (Usui, et al. 2001)
Phenolphthalein	77-09-8	2B	Reasonable	+;+;+;+ f (NTP 1995c)	-;+	+ f;+ f (Dunnick, et al. 1997)	nt	- f (Koujitani, et al. 2000)
4-Vinyl-1-cyclohexene diepoxide	106-87-6	2B	Reasonable	+;+;+;+ d (NTP 1989a)	+;+	+ d (Tennant, et al. 1995)	- d (Tennant, et al. 1999)	+ d (Yamamoto, et al. 1998b)
2,4-Diaminotolulene	95-80-7	2B	Reasonable	+;+;-;+ f (NCI/NTP 1979a)	+;-	± f (Eastin, et al. 1998)	+ d (Eastin, et al. 1998)	nt
Chloroprene	126-99-8	2B	Reasonable	+;+;+;+ I (NTP 1998b)	-;-	- i (French 2001)	- i (French 2001)	nt
Pentachlorophenol	87-86-5	2B	Not Listed	+[2];-;+;+ f (NTP 1999f)	-;-	- f (Spalding, et al. 2000)	+ d (Spalding, et al. 2000)	nt
Phenacetin	62-44-2	2A	Reasonable	nt	-;nt	- f; - g (Storer, et al. 2001)	-d; -f (Eastin, et al. 2001)	+ f (Yamamoto, et al. 1998b)
Phenobarbital	50-06-6	2B	Not Listed	nt	wk+;nt	- f;- f (Sagartz, et al. 1998;Storer, et al. 2001)	ia d; ia g; ia f (Eastin, et al. 2001)	-g (Usui, et al. 2001)
Chloroform	67-66-3	2B	Reasonable	+;-;+;+ w (Griesemer and Cueto 1980)	-;+	± g (Storer, et al. 2001)	- g (Delker, et al. 1999)	- g (Usui, et al. 2001)

[1] "Probable" (2A) or "possible" (2B) human or "reasonably anticipated" to be a human carcinogen as identified by the International Agency for Research on Cancer (IARC) and/or NTP Report on Carcinogens (9th NTP ROC, revised January 2001), respectively.

[2] Positive in 1000 ppm 1 year exposure stop study but not with 2 year exposure to technical grade pentachlorophenol (technical grade, TR349; purified, TR483)

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
Benzo[a]pyrene	50-32-8	2A	Reasonable	nt	+;nt	+ d,g (Martin, et al. 2001)	+ d (Martin, et al. 2001)	nt
Dimethylnitrosamine	62-75-9	2A	Not Listed	nt	+;nt	+ w (Harvey, et al. 1993)	nt	nt
7,12-Dimethylbenzanthracene[3]	57-97-6	NE	Not Listed	nt;nt;+;+ d, i-p (NTP 1996)	+;+	+ d (Kemp, et al. 1993)	+ d (Spalding, et al. 1993)	nt
N-ethyl-N-nitrosourea	759-73-9	2A	Not Listed	nt	+;+	+ ip (Mitsumori, et al. 2000)	nt	+ ip (Yamamoto, et al. 1998b)
2-Amino-3-methylimidazo[4,5-f]quinoline	76180-96-6	2A	Not Listed	nt	+;+	+ g (Nagao 1999)	nt	nt
N-Butyl-N-(4-hydroxybutyl) nitrosamine (BBN)	64091-91-4	2B	Not Listed	nt	nt;-	+ w (Ozaki, et al. 1998)	nt	nt
N-methyl-N-nitrosourea	684-93-5	2A	Not Listed	nt	nt;+	+ip (Yamamoto, et al. 2000)	nt	+ ip (Yamamoto, et al. 1998b)
Urethane	51-79-6 5	2B	Reasonable	nt	+;+	+ ip (Carmichael, et al. 2000)	+d (Spalding, et al. 1993)	+ ip (Mori, et al. 2000;Umemura , et al. 1999)
Oxymetholone	434-07-1	2A	Reasonable	±;+;nt;nt (NTP 1999e)	-;-	- g (Stoll, et al. 1999)	+ d (Stoll, et al. 1999)	nt
1, 2-Dimethylhydrazine	540-73-8	2A	Not listed	nt	-[4];nt	nt	nt	+ d (Yamamoto, et al. 1998b)
1,4-Dioxane	123-91-1	2B	Reasonable	+;+;+;+ w (NCI/NTP 1978b)	-;+	nt	nt	± w (Yamamoto, et al. 1998b)
Ethylene thiourea	96-45-7	2B	Reasonable	+;+;+;+ f (NTP 1992a)	-;nt	nt	nt	+f (Yamamoto, et al. 1998b)
Methylazoxymethanol acetate	592-62-1	2B	Not listed	nt	-;nt	nt	nt	+ sc (Yamamoto, et al. 1998b)

[3] Reasonably anticipated to be a human carcinogen based on its use a prototypical mutagenic carcinogen used in initiation-promotion and complete carcinogenicity studies.
[4] 1,2-dimethylhydrazine dihydrochloride (CAS No. 306-37-6) tested in *Salmonella* mutagenicity assay.

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
Procarbazine	366-70-1	2A	Reasonable	+;+;+;+ ip (NCI/NTP 1979d)	+;+	nt	nt	+ip (Yamamoto, et al. 1998b)
4,4'-Thiodianiline	139-65-1	2B	Not listed	+;+;+;+ f (NCI/NTP 1978c)	+;nt	nt	nt	+f (Yamamoto, et al. 1998b)
MNNG	70-25-7	2A	Reasonable	+;+;+ d ip (NTP 1996)	+;nt	nt	nt	+ g (Yamamoto, et al. 1998b)
Cupferron	135-20-6	2A	Reasonable	+;+;+;+ f (NCI/NTP 1978d)	+;nt	nt	nt	+ f (Yamamoto, et al. 1998b)
N-nitrosodiethylamine	55-18-5	2A	Reasonable	nt	+;nt	nt	nt	+ ip (Yamamoto, et al. 1998b)
Dimethylvinylchloride	513-37-1	2B	Not listed	+;+;+;+ g (NTP 1986b)	+;+	nt	+ d (Stoll, et al. 1999)	nt
4-Nitroquinoline N-oxide[5]	56-57-5	NE	Not listed	nt	+;nt	nt	nt	+sc (Yamamoto, et al. 1998b)
4-Hydroxyaminoquinoline-1-oxide[5]	4637-56-3	NE	Not listed	nt	+;nt	nt	nt	+ ip (Yamamoto, et al. 1998b)
Mirex	2385-85-5	2B	Reasonable	+;+;nt;nt f (NTP 1990d)	-;nt	nt	+d (Stoll, et al. 1999)	nt

[5] Reasonably anticipated to be a human carcinogen based upon its use as a prototypical mutagenic carcinogen for mechanistic investigation of chemical carcinogenesis.

Table 3. Comparison of results from 52 suspected human carcinogens[1] tested in rodent NCI/NTP cancer bioassays, Salmonella and/or in vivo micronuclei genotoxicity assays and/or 3 transgenic mouse bioassays. Individual results are found in the cited references in parenthesis or in the IARC(IARC 2002) or in the US NTP database(NTP 2002). NCI/NTP Peer-reviewed conclusions are reported for male F344 rat, female F344 rat, male B6C3F1 mouse; or female B6C3F1 mouse, respectively. Results from transgenic models are presented as the summary conclusion for each route of exposure using one or both sexes.; w, water (routes of exposure); nt, not tested or no published record.

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
p-Anisidine	90-04-0	3	Not Listed	±;-;-;- f, (NCI/NTP 1978e)	+;-	- f (Tennant, et al. 1995)	- d (Tennant, et al. 1995)	- g (Maronpot, et al. 2000)
1-Chloro-2-propanol	127-00-4	NE	Not Listed	-;-;-;- w (NTP 1998a)	+;nt	- g (Tennant, et al. 1999)	- d (Tennant, et al. 1999)	nt
2,6-Diaminotoluene	820-40-5	NE	Not Listed	-;-;-;- f (Battershill and Fielder 1998)	+;-	- f (Eastin, et al. 1998)	- d(Eastin, et al. 1998)	nt
8-Hydroxyquinoline	148-24-3	3	Not Listed	-;-;-;- f (NTP 1985b)	+;-	-f (Eastin, et al. 1998)	-d (Eastin, et al. 1998)	nt
Coconut oil diethanolamine	68603-42-9	NE	Not Listed	-; ±;+;+ d (NTP 2001)	-;+	- d (Spalding, et al. 2000)	- d (Spalding, et al. 2000)	nt
Diethanolamine	111-42-2	3	Not Listed	-;-;+;+ d (NTP 1999h)	-;-	nt	- d (Spalding, et al. 2000)	nt
Ethyl Acrylate	140-88-5	2B	Delisted	+;+;+;+ g (NTP 1986a)	-;-	nt	- d (Nylander-French and French 1998;Tice, et al. 1997)	+ g (Yamamoto, et al. 1998b)
Furfuryl alcohol	98-00-0	NE	Not Listed	+; ±;+;- i (NTP 1999a)	-;-	nt	- d (Spalding, et al. 2000)	nt
Lauric acid diethanolamine	120-40-1	NE	Not Listed	-;-;-;+ d (NTP 1999b)	-;-	-f (Spalding, et al. 2000)	+ d (Spalding, et al. 2000)	nt
N-methyloacrylamide	924-42-5	3	Not Listed	-;-;+;+ g (NTP 1989b)	-;-	-g (Tennant, et al. 1995)	- d; - g (Eastin, et al. 1998)	nt
Methylphenidate	298-59-9	NE	Not Listed	-;-;+;+ f (NTP 1995a)	-;nt	-f (Tennant, et al. 1999)	- d (Tennant, et al. 1999)	nt
Pyridine	110-86-1	3	Not Listed	+;±;+;+ w (NTP 2000)	-;-	-g (Spalding, et al. 2000)	- d (Spalding, et al. 2000)	nt
Reserpine	50-55-5	3	Reasonable	+;-:+;+ f (NCI/NTP 1982a)	-;-	-f (Tennant, et al. 1995)	-d;-g (Tennant, et al. 1995)	- f (24)
Rotenone	83-79-4	NE	Not Listed	±;-;-;- f (NTP 1988b)	-;nt	- f (Eastin, et al. 1998)	+ d;- g (Eastin, et al. 1998)	- g (Yamamoto, et al. 1998b)

[1] "Probable" (2A) or "possible" (2B) human or "reasonably anticipated" to be a human carcinogen as identified by the International Agency for Research on Cancer (IARC) and/or NTP Report on Carcinogens (9th NTP ROC, revised January 2001), respectively.

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
Resorcinol	108-46-3	3	Not Listed	-;-;-;- g (NTP 1992b)	-;+	- g (Eastin, et al. 1998)	+ d (Eastin, et al. 1998)	- g (Maronpot, et al. 2000)
Oleic acid diethanolamide	93-83-4	NE	Not Listed	-;-;-;- d (NTP 1999d)	-; nt	- d (Spalding, et al. 2000)	- d (Spalding, et al. 2000)	nt
Clolfibrate	637-07-0	3	Not Listed	nt	-;-	- g; - g (Storer, et al. 2001)	+d (Eastin, et al. 2001)	± g; + g (Usui, et al. 2001)
Dieldrin	60-57-1	3	Not Listed	-;-;±;- f (NCI/NTP 1978g)	-;nt	- f (Storer, et al. 2001)	nt	- f (Usui, et al. 2001)
Methapyrilene HCl	135-23-9	NE	Not Listed	+;+;nt;nt f (W Lijinsky 1080)	-;-	- g;-f (Storer, et al. 2001)	-d (Eastin, et al. 2001)	- g (Yamamoto, et al. 1996)
Haloperidol	52-86-8	NE	Not Listed	nt	nt;nt	- g (Storer, et al. 2001)	nt	- g (Usui, et al. 2001)
Chlorpromazine HCl	69-09-0	NE	Not Listed	nt	-;nt	- g;-g (Storer, et al. 2001)	nt	- g (Usui, et al. 2001)
Metaproterenol	586-06-1	NE	Not Listed	nt	nt;nt	- f;-f (Storer, et al. 2001)	nt	- f (24)
WY-14643	50892-23-4	NE	Not Listed	nt	nt;nt	- f (Storer, et al. 2001)	-d; ±f (Eastin, et al. 2001)	nt
Di(2-ethylhexyl)phthalate	117-81-7	3	Reasonable	+;+;+;+ f (NTP 1982)	-;-	± f (Storer, et al. 2001)	-d; -f (Eastin, et al. 2001)	+ (Usui, et al. 2001)
Sulfamethoxazole	723-46-6	3	Not Listed	nt	-;nt	- f (Storer, et al. 2001)	-d; -g (Eastin, et al. 2001)	-f (Usui, et al. 2001)
Sulfisoxazole	127-69-5	3	Not Listed	-;-;-l;- f (NCI/NTP 1979e)	-;nt	- f (Storer, et al. 2001)	- d;-g (Eastin, et al. 2001)	-f (Usui, et al. 2001)
Ampicillin	7177-48-2	3	Not Listed	±;-;-;- f (NTP 1987)	-;nt	- g (Storer, et al. 2001)	nt	-g (Usui, et al. 2001)
D-Mannitol	69-65-8	NE	Not Listed	-;-;-;- f (NCI/NTP 1982c)	-;-	-f (Storer, et al. 2001)	nt	- f (24)
1,1,2-Trichloroethane	79-00-5	3	Not Listed	-;-;+;+ g (NCI/NTP 1978a)	-;-	nt	nt	+ g (Yamamoto, et al. 1998b)
Xylenes (mixed)	1330-20-7	3	Not Listed	-;-;-;-;- g (NTP 1986c)	-;nt	nt	nt	- g (Yamamoto, et al. 1998b)
Furfural	98-01-1	3	Not Listed	+;-;+;+ g (NTP 1990b)	-;nt	nt	nt	+ g (Yamamoto, et al. 1998b)
5-Nitro-o-toluidine	99-55-8	3	Not Listed	-;-;+;+ f (NCI/NTP 19778)	+;nt	nt	nt	+f (Yamamoto, et al. 1998b)
Benzethonium chloride	121-54-0	NE	Not Listed	-;-;-;- d (NTP 1995b)	-;nt	nt	- d (Spalding, et al. 1999)	nt
o-Benzyl-*p*-chlorophenol	120-32-1	NE	Not Listed	-;±;+;- g (NTP 1994)	-;nt	nt	+ d (Spalding, et al. 1999)	nt

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
2-Chloroethanol	107-07-3	NE	Not Listed	-;-;-;- d (NTP 1985a)	+;-	nt	- d (Spalding, et al. 1999)	nt
Phenol	108-95-2	3	Not Listed	-;-;-;- dw (NCI/NTP 1980)	-;+	nt	-d (Spalding, et al. 1999)	nt
Triethanolamine	102-71-6	3	Not Listed	±;-;ia;ia d (NTP 1999g)	-;-	nt	-d (Spalding, et al. 1999)	nt
Acetic anhydride	108-24-7	NE	Not Listed	nt	-;nt	nt	-d (Spalding, et al. 1999)	nt
2,4-dinitro-1-fluorobenzene	70-34-8	NE	Not Listed	nt	+;nt	nt	+d (Albert, et al. 1996)	nt
Diisopropylcarbodiimide	693-13-0	NE	Not Listed	in progress	-;+	in progress	+d (Spalding, et al. 1999)	nt
Dicyclohexylcarbodiimide	538-75-0	NE	Not Listed	In progress	+;+	nt	-d (Spalding, et al. 1999)	nt
Fluocinolone acetonide	67-73-2	NE	Not Listed	nt	nt;nt	nt	- d (Albert, et al. 1996)	nt
Tripropylene Glycol Diacrylate	42978-66-5	NE	Not Listed	nt	-;-	nt	+ d(Albert, et al. 1996)	nt
d-Limonene	5989-27-5	3	Not Listed	+'-;-;- f (NTP 1990a)	-;nt	- g (Carmichael, et al. 2000)	nt	nt
Foreign body (transponder)	NA	NE	Not Listed	nt	-;-	+ sc (Blanchard, et al. 1999)	- sc (French 2001)	nt
Acetone	67-64-1	NE	Not Listed	nt	-;-	nt	- d (Spalding, et al. 1999;Spalding, et al. 1993)	nt
Benzoyl peroxide	94-36-0	3	Not Listed	+ i-p[2] (NTP 1996)	-;nt	nt	+ d (Spalding, et al. 1993)	nt
Ethanol[3]	64-17-5	NE	Not Listed	in progress	-;nt	nt	- d (Spalding, et al. 1999)	nt
Methyl ethyl ketone peroxide	1338-23-4	NE	Not Listed	in progress	+;-	nt	+ d (Spalding, et al. 1993)	nt
4-Nitro-o-phenylenediamine	99-56-9	3	Not Listed	-;-;-;- f (NCI/NTP 1979b)	+; inc	nt	nt	± f (Yamamoto, et al. 1998b)
6-Nitrobenzimidazole	94-52-0	NE	Not Listed	-;-;+;+ f (NCI/NTP 1979c)	+;nt	nt	nt	- f (Yamamoto, et al. 1998b)

[2] Results from initiation-promotion studies in B6C3F1, Swiss (CD-1), and SENCAR mice (see reference 85).

Agent	CAS No.	IARC	NTP ROC	NCI/NTP Bioassays	Genotoxicity (Sal; Mn)	p53+/-	Tg.AC	RasH2
Cholestyramine	11041-12-6	NE	Not Listed	nt	nt; nt	nt	nt	- f (Yamamoto, et al. 1998b)
60 mHz Magnetic fields	NA	NE	Not Listed	-;-;-;-wb (NTP 1999c)	-;-	- wb (McCormick, et al. 1998)	- wb (McCormick, et al. 1998)	nt

Table 4. Summary performance of each strategy versus likely human cancer. All chemicals in Tables 1 and 2 are included as human carcinogens, but only those chemicals in Table 3 with negative NCI/NTP bioassay results are regarded as true human noncarcinogens.

Strategy	Positive for Carcinogens	Negative for Noncarcinogens	Positive for Noncarcinogens	Negative for Carcinogens	Overall Accuracy
(1) Trp53+/-	21	12	0	10	77 % (33/43)
(2) Trp53+/- (genotoxic)	16	5	0	4	84 % (21/25)
(3) Tg.AC	17	11	2	6	78 % (28/36)
(4) RasH2	21	9	0	7	81 % (30/37)
(5) Trp53+/- (genotoxic); RasH2 (nongenotoxic)	18	7	0	7	78 % (25/32)
(6) Trp53+/- (genotoxic); RasH2 (all)	31	7	0	5	88 % (38/43)
(7) Trp53+/- (genotoxic); Tg.AC (nongenotoxic)	21	9	0	6	83 % (30/36)
(8) Trp53+/- (genotoxic); Tg.AC for all	25	8	2	4	85 % (33/39)

Definitions

Positive for Carcinogens	=	Positive assay results for IARC/ROC carcinogens
Negative for Noncarcinogens	=	Negative assay results for IARC/ROC noncarcinogens
Positive for Noncarcinogens	=	Positive assay results for IARC/ROC noncarcinogens
Negative for Carcinogens	=	Negative assay results for IARC/ROC carcinogens

Table 5. Proportion of positive responses in the three transgenic models as a function of the IARC classification of these 99 chemicals.

IARC Classification	Trp53+/-	Tg.AC	RasH2	Overall
Group 1	83 % (10/12)	89 % (8/9)	57 % (4/7)[1]	79 % (22/28)
Group 2A	62 % (5/8)	50 % (2/4)	100 % (9/9)	76 % (16/21)
Group 2B[2]	55 % (6/11)	64 % (7/11)	69 % (9/13)	63 % (22/35)
Group 3	0 % (0/13)	21 % (3/14)	36 % (5/14)	20 % (8/41)
Not Evaluated	7 % (1/15)	29 % (7/24)	0 % (0/8)	17 % (8/47)

[1] Two of the three that were not positive were equivocal.

[2] Includes 7,12-dimethylbenzanthracene, 4-nitroquinoline N-oxide, and 4-hydroxyaminoquinoline-1-oxide.

Table 6. Summary of performance of each Strategy versus likely human cancer when all chemicals in Table 3 are regarded as true human non-carcinogens.

Strategy	Positive for Carcinogens	Negative for Noncarcinogens	Positive for Noncarcinogens	Negative for Carcinogens	Overall Accuracy
(1) Trp53+/-	21	27	1	10	81 % (48/59)
(2) Trp53+/- (genotoxic)	16	6	0	4	85 % (22/26)
(3) Tg.AC	17	29	10	6	74 % (44/62)
(4) RasH2	21	17	6	7	75 % (38/51)
(5) Trp53+/- (genotoxic); RasH2 (nongenotoxic)	18	17	1	7	81 % (35/43)
(6) Trp53+/- (genotoxic); RasH2 (all)	30	13	6	5	80 % (43/54)
(7) Trp53+/- (genotoxic); Tg.AC (nongenotoxic)	21	21	1	6	86 % (42/49)
(8) Trp53+/- (genotoxic); Tg.AC for all	25	20	10	5	75 % (45/60)
(9) NTP Rodent Bioassay	23	17	18	0	69 % (40/58)
(10) NTP Rat Bioassay; Tg.AC (nongenotoxic); Trp53+/- (genotoxic)	35	13	9	0	84 % (48/57)
(11) NTP Rat Bioassay; RasH2 (nongenotoxic); Trp53+/- (genotoxic)	33	11	8	0	85 % (44/52)
(12) NTP Rat Bioassay; genotoxicity	36	7	23	0	65 % (43/66)

Table 7. Summary performance of each strategy (vs. NTP rodent cancer results)

Strategy	Positive for Carcinogens	Negative for Noncarcinogens	Positive for Noncarcinogens	Negative for Carcinogens	Overall Accuracy
(1) Trp53+/-	7	12	0	16	54 % (19/35)
(2) Trp53+/- (genotoxic)	7	5	0	4	75 % (12/16)
(3) Tg.AC	14	10	2	14	60 % (24/40)
(4) RasH2	16	9	0	7	78 % (25/32)
(5) Trp53+/- (genotoxic); RasH2 (nongenotoxic)	9	10	0	7	73 % (19/26)
(6) Trp53+/- (genotoxic); RasH2 (all)	19	7	0	3	90 % (26/29)
(7) Trp53+/- (genotoxic); Tg.AC (nongenotoxic)	10	8	0	13	58 % (18/31)
(8) Trp53+/- (genotoxic); Tg.AC for all	15	7	2	12	61 % (22/36)

EXHIBIT 49

Exhibit 49: Defendants' Sales and Holdings of Connetics Stock Between January 27, 2004 and July 9, 2006

Defendant	Stock Sales (shares)	Holdings Remaining (shares)[1]	Percent of Total Holdings Sold[2]
John L. Higgins	130,517[3]	603,625	17.8%
Lincoln Krochmal	None[4]	214,193	0%
C. Gregory Vontz	32,279[5]	737,707	4.2%
Thomas G. Wiggans	190,380[6]	1,526,247	11.1%
Aggregate Total	353,176	3,081,772	10.3%

[1] This column reflects the common stock and "exercisable" options held by each defendant as of May 23, 2006, as reported in Connetics' 2006 proxy statement. Ex. 25, at 9. May 23, 2006 is also the most appropriate date to use for assessing defendants' holdings because it is nearly three months after the last sales transaction involving direct monetary compensation challenged by plaintiff (*i.e.*, on March 1, 2006). SAC ¶ 328. *See also* footnote 5 *infra.*

[2] This column reflects each defendant's sales of common stock and exercisable options during the purported class period January 27, 2004 to July 9, 2006 as a percentage of his total holdings. The percentage is arrived at by: (1) adding the number of shares sold to the remaining shares held as of May 23, 2006 to determine each defendants' total holdings during the class period ("Total Holdings"); and (2) dividing the number of shares sold during the class period by the Total Holdings to determine the percentage of holdings sold. For example, the amount of Mr. Higgins' total holdings is 734,142 shares, which is calculated by adding his stock sales during the class period (130,517 shares) and his holdings remaining as of May 23, 2006 (603,625). The percentage of total holdings is 17.8%, which is calculated by dividing Mr. Higgins' stock sales (130,517 shares) by his total holdings (734,142 shares). SAC ¶ 328; Ex. 22.

[3] SAC ¶ 328; Ex. 22. As demonstrated by Mr. Higgans' Forms 4 (Ex. 22), Mr. Higgans actually ***acquired*** more shares of Connetics' stock than he sold during the Class Period.

[4] SAC ¶ 328; Ex. 24.

[5] SAC ¶ 328; Ex. 23.

[6] Plaintiff's calculation of Mr. Wiggans' class period sales includes six transactions which were actually gifts to educational institutions, from which Mr. Wiggans derived no direct monetary compensation. *See* SAC ¶ 328; Ex. 21. The calculation in this chart includes the total number of shares sold by Wiggans for monetary value. *Id.* If the gift transactions are also included, the total stock sales (shares) in the class period by Wiggans is 205,280 and the percentage of total holdings sold is 11.9%. *Id.*

Exhibit 49 (con't): Defendants' Sales of Connetics Stock Between July 1, 2001 and January 26, 2004

	Thomas G. Wiggans (shares)[1]	John L. Higgins (shares)[2]	C. Gregory Vontz (shares)[3]
Jan. 2004	2,000	25,000*	--
Dec. 2003	--	--	15,000*
Nov. 2003	713	2,184	--
Oct. 2003	15,000*	10,000*	--
Sept. 2003	5,000	5,120	14,910*
Aug. 2003	--	--	--
July 2003	15,000*	--	--
June 2003	--	--	--
May 2003	350	--	--
Apr. 2003	15,000*	8,000*	--
Mar. 2003	16,000*	7,000*	--
Feb. 2003	15,000*	5,000* 6,095 7,000	--
Jan. 2003	--	--	--
Dec. 2002	7,000	6,000*	--
Nov. 2002	--	--	--
Oct. 2002	--	5,000*	--
Sept. 2002	--	--	--
Aug. 2002	15,000*	4,000*	--
July 2002	--	--	25,000
June 2002	--	3,000*	--
May 2002	15,000*	--	--
Apr. 2002	--	2,000*	--
Mar. 2002	15,000*	--	--
Feb. 2002	--	--	--
Jan. 2002	--	--	--
Dec. 2001	6,500	--	--
July - Nov. 2001			
Total	**142,563 Shares**	**95,399 Shares**	**54,910 Shares**

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* Sale pursuant to plan adopted under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended. The Forms 4 reflecting each defendant's sales indicate whether the sales were made pursuant to a Rule 10b5-1 trading plan. Exs. 21-24.

[1] Exhibit 21 contains each Form 4 filed reflecting a stock sale by Mr. Wiggans.

[2] Exhibit 22 contains each Form 4 filed reflecting a stock sale by Mr. Higgins.

[3] Exhibit 23 contains each Form 4 filed reflecting a stock sale by Mr. Vontz.

EXHIBIT 50

Exhibit 50: Meaningful Cautionary Language Publicly Disclosed by Connetics Corp. Regarding Velac

Source(s)	Meaningful Cautionary Language
Ex. 3, at 18; Ex. 4, at 20; Ex. 5, at 24; Ex. 6, at 23; Ex. 7, at 32 (Forms 10-K) (emphasis in original)	"***We may spend a significant amount of money to obtain FDA and other regulatory approvals, which may never be granted. Failure to obtain such regulatory approvals could adversely affect our prospects for future revenue growth***"
Ex. 3, at 33 (Form 10-K/A) (emphasis added)	"***We are subject to uncertainties associated with product development and market acceptance.*** We have several product candidates in clinical or preclinical development. ***Products under development may not be safe and effective or approved by the FDA*** . . . ."
Ex. 3, at 10; Ex. 4, at 11; Ex. 5, at 14; Ex. 6, at 14 (Forms 10-K) (emphasis added)	"We must receive FDA clearance before we can commercialize the product, and ***the FDA may not grant approval*** on a timely basis or at all."
Ex. 3, at 10; Ex. 4, at 11; Ex. 5, at 14; Ex. 6, at 14 (Forms 10-K) (emphasis added)	***"We may not obtain regulatory approval*** for any products that we develop, even after committing such time and expenditures to the process."
Ex. 3, at 17; Ex. 4, at 19; Ex. 5, at 23; Ex. 6, at 22 (Forms 10-K) (emphasis added)	***"The process of obtaining and maintaining regulatory approvals*** for pharmaceutical products, and obtaining and maintaining regulatory approvals to market these products for new indications, ***is lengthy, expensive and uncertain."***
Ex. 3, at 18; Ex. 4, at 20; Ex. 5, at 24; Ex. 6, at 23 (Forms 10-K) (emphasis added)	"Successful product development in our industry is highly uncertain, and the process of obtaining FDA and other regulatory approvals is lengthy and expensive. Very few research and development projects produce a commercial product. ***Product candidates that appear promising in the early phases of development may fail to reach the market for a number of reasons . . . . The FDA approval processes require substantial time and effort, the FDA continues to modify product development guidelines, and the FDA may not grant approval on a timely basis or at all. Clinical trial data can be the subject of differing interpretation, and the FDA has substantial discretion in the approval process.*** The FDA may not interpret our clinical data the way we do . . . . We may not be able to obtain FDA approval to conduct

Source(s)	Meaningful Cautionary Language
	clinical trials or to manufacture and market any of the products we develop, acquire or license."
Ex. 12 (Form 8-K) (emphasis added)	"Such statements are subject to a number of assumptions, risks and uncertainties, many of which are beyond Connetics' control, and which could cause actual results or events to differ materially from those expressed in such forward-looking statements. . . . ***In particular, Connetics faces risks and uncertainties that . . . Velac may not be approved by the FDA in the time frames projected, if at all*** . . . . Factors that could cause or contribute to such differences include, but are not limited to, risks and other factors that are discussed in documents filed by Connetics with the Securities and Exchange Commission from time to time . . . ." (emphasis added)
Ex. 8 (Form 8-K) (emphasis added)	"This news release contains forward-looking statements . . . subject to risks and uncertainties that could cause actual results or events to differ materially from those expressed in such forward-looking statements. . . . ***In particular, Connetics faces risks and uncertainties that U.S. development of Velac(R) may not succeed, that Velac(R) may not be approved for marketing in the U.S.***, that clinical trials of the product may not produce the same results as shown in earlier clinical trials, that physicians may not respond as favorably as anticipated to the product, that future sales of Velac(R) may not be as robust as anticipated . . . and that clinical trials may not go forward as planned. The actual results could differ materially from those contained in the forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, risks and other factors that are discussed in documents filed by Connetics with the Securities and Exchange Commission from time to time . . . ."
Ex. 9 (Form 8-K) (emphasis added)	"This news release includes forward-looking statements, and predictions, including statements about . . . the market potential of certain products and product candidates, and the potential value of pipeline products. These statements . . . are subject to risks and uncertainties that could cause actual results or events to differ materially from those expressed in such forward-looking statements. ***In particular, Connetics faces risks and uncertainties . . . that development of product candidates in the Company's pipeline may not succeed or that clinical trials may not go forward as planned*** . . . . Factors that could cause or contribute to such differences include, but are not limited to, risks and other factors that are discussed in documents filed by Connetics with the Securities and Exchange Commission from time to time . . . ."
Ex. 3, at 1; Ex. 5, at 1; Ex. 6, at 1; (Forms 10-K) (emphasis added)	"Although we believe that our plans, intentions and expectations reflected in these forward-looking statements are reasonable, we may not achieve these plans, intentions or expectations. ***Forward-looking statements in this Report include, but are not limited to, those relating to the . . . developments with***

Source(s)	Meaningful Cautionary Language
	respect to clinical trials and the regulatory approval process . . . . Actual results, performance or achievements could differ materially from those contemplated, expressed or implied by the forward-looking statements contained in this Report. Important factors that could cause actual results to differ materially from our forward-looking statements are set forth in this Report. These factors are not intended to represent a complete list of the general or specific factors that may affect us."
Ex. 10 (Form 8-K) (emphasis added)	"All statements included in this press release that address activities, events or developments that Connetics expects, believes or anticipates will or may occur in the future are forward-looking statements, ***including specifically comments about the timing of filing an NDA, the market potential for Velac, and the likelihood of approval of Velac.*** These statements are based on certain assumptions made by Connetics' management based on experience and perception of historical trends, current conditions, expected future developments and other factors it believes are appropriate in the circumstances. Such statements are subject to a number of assumptions, risks and uncertainties, many of which are beyond Connetics' control, and which could cause actual results or events to differ materially from those expressed in such forward-looking statements. Any such projections or statements include Connetics' current views with respect to future events and financial performance. No assurances can be given, however, that these events will occur or that such results will be achieved. Factors that could cause or contribute to such differences include, but are not limited to, risks and other factors that are discussed in documents filed by Connetics with the Securities and Exchange Commission from time to time . . . ."
Ex. 15 (Form 8-K) (emphasis added)	"***Statements pertaining to revenue expectations, revenue growth, and sales and marketing success of, and regulatory and clinical milestones associated with, Connetics' products or product candidates are also forward-looking statements.*** These forward-looking statements are based on certain assumptions made by Connetics' management based on its experience and perception of historical trends, current conditions, expected future developments and other factors it believes are appropriate in the circumstances. Such statements are subject to a number of assumptions, risks and uncertainties, many of which are beyond Connetics' control, and which could cause actual results or events to differ materially from those expressed in such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, risks and other factors that are discussed in documents filed by Connetics with the Securities and Exchange Commission from time to time . . . ."
Ex. 16 (Form 8-K) (emphasis added)	"***Statements about the impact of the non-approvable letter from the FDA to our business, our future plans for Velac, and projections for revenues and earnings for 2005 are forward-looking statements.*** These statements are based on certain assumptions made by Connetics' management based on experience

Source(s)	Meaningful Cautionary Language
	and perception of historical trends, current conditions, expected future developments and other factors it believes are appropriate in the circumstances. Such statements are subject to a number of assumptions, risks and uncertainties, many of which are beyond Connetics' control, and which could cause actual results or events to differ materially from those expressed in such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, risks and other factors that are discussed in documents filed by Connetics with the Securities and Exchange Commission from time to time . . . ."
Ex. 1 (analyst call transcript)	"Our remarks and responses to questions during this conference call may constitute forward-looking statements, including plans, expectations and projections, all of which involve certain assumptions, risks and uncertainties that are beyond our control. And could cause our actual results to differ materially from these statements. Those risks and uncertainties include among others, that sales growth and future product revenues may be lower or expenses may be higher than our projections in any quarter. ***And that our clinical and regulatory expectations for our product candidates, including approval timeframes we expect, may not be met.*** And that the company may not be able to sustain profitability. We encourage you to take the time to review our recent filings with the Securities and Exchange Commission and the first quarter earnings release issued earlier today, which present these matters in more detail . . . ."

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